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American Heart Journal

Vol. 47 April, 1954 No. 4

Original Communications

THE SPATIAL VECTORCARDIOGRAM IN MYOCARDIAL INFARCTION TYPIFIED BY PROMINENT R WAVES IN LEADS aV_R AND V_1

Stephen R. Elek, M.D., B. J. Allenstein, M.D., A. W. Kornbluth, M.D., George C. Griffith, M.D., and David C. Levinson, M.D.

Los Angeles, Calif.

The purpose of this paper is to emphasize the vectorcardiographic features and significance of myocardial infarction distinguished by the presence of prominent R waves in Leads aV_R and/or V_1. This usually occurs in antero- or posterolateral myocardial infarction; curiously, only a few reports have appeared on this subject limited to the electrocardiographic aspects.

Levy and co-workers[1] reported twelve such cases with clinical and electrocardiographic evidence; ten cases had a prominent R wave and shallow S wave in Lead V_1 only, and two cases with posterolateral infarction had prominent R waves in both Leads aV_R and V_1. Eight of the infarcts were posterolateral, one was anterolateral, and three were posterior. Tulloch[2] has recently reported thirteen cases of high posterolateral myocardial infarction, four of whom were necropsied. He found the following electrocardiographic pattern: (a) predominant R wave in Lead V_1; (b) absence of a definite transitional zone in the precordial leads; (c) tall T waves in two or more precordial leads (usually V_1 to V_3); and (d) depressed S-T segments in the precordial leads in the acute stages; Leads V_5 and V_6 usually showed the infarct.

Myers and co-workers[3-6] have reported one hundred-sixty cases of myocardial infarction verified by necropsy. Their work was reviewed in an effort to correlate the size of the infarct with the presence of prominent R wave in the right-sided leads. There were one hundred-five cases of large lateral wall infarction that involved the anterior and/or posterior myocardium as well. Of the

From the Department of Medicine (Cardiology), School of Medicine, University of Southern California, and the Los Angeles County Hospital, Los Angeles, Calif.

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eighty-six described in detail, there were eighteen cases in which the R wave was prominent in the right-sided leads divided as follows: in nine cases with large posterolateral infarction, the R wave was prominent in both aV_R and V_1; in the remaining nine cases the R wave was prominent in aV_R only and the posterior myocardium was little, if any, involved. However, all eighteen cases had one common feature at necropsy: the infarcted area was large in proportion to the remaining left ventricular myocardium.

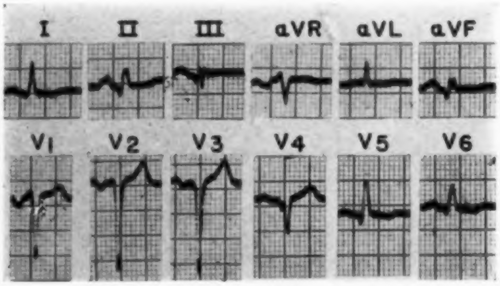

Fig. 1A.—Electrocardiogram of patient H.M. taken on July 21, 1950 shows an old posterior wall infarct and recent anteroseptal infarct.

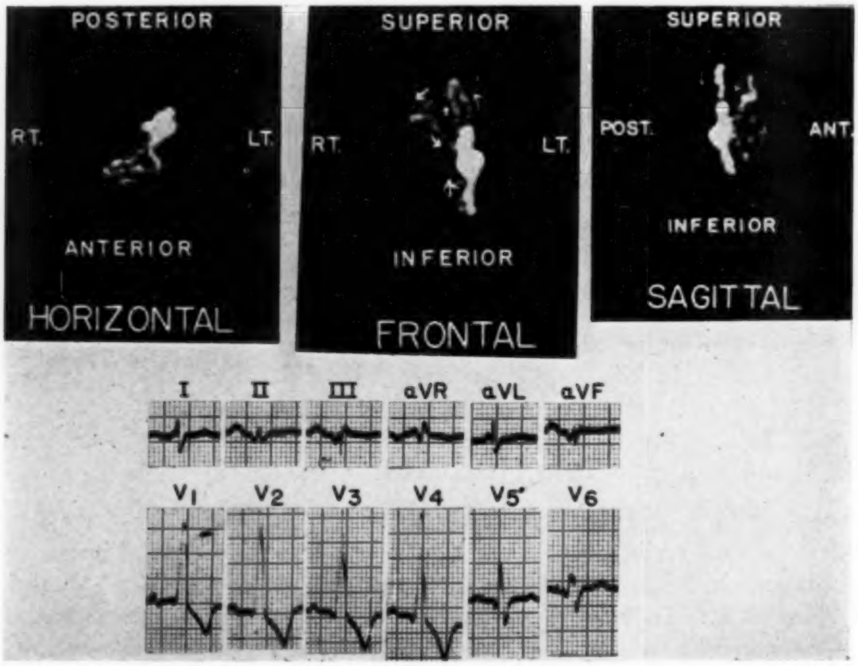

Fig. 1B.—Electrocardiogram of patient H.M. taken on Oct. 17, 1952 shows more recent posterior wall infarct and development of prominent R waves in Leads aV_R and V_1. The vectorcardiogram is in the right superior anterior octant. See text.

The vectorcardiographic study of myocardial infarction by Scherlis and coworkers[7] and Grishman and Scherlis[8] revealed ten patients with prominent R waves in the right-sided leads; they had anterolateral or posterolateral infarction.

In this publication, we are reporting on five cases with the above mentioned prominent R waves selected from ninety-six cases of myocardial infarction studied by the direct spatial vectorcardiogram.

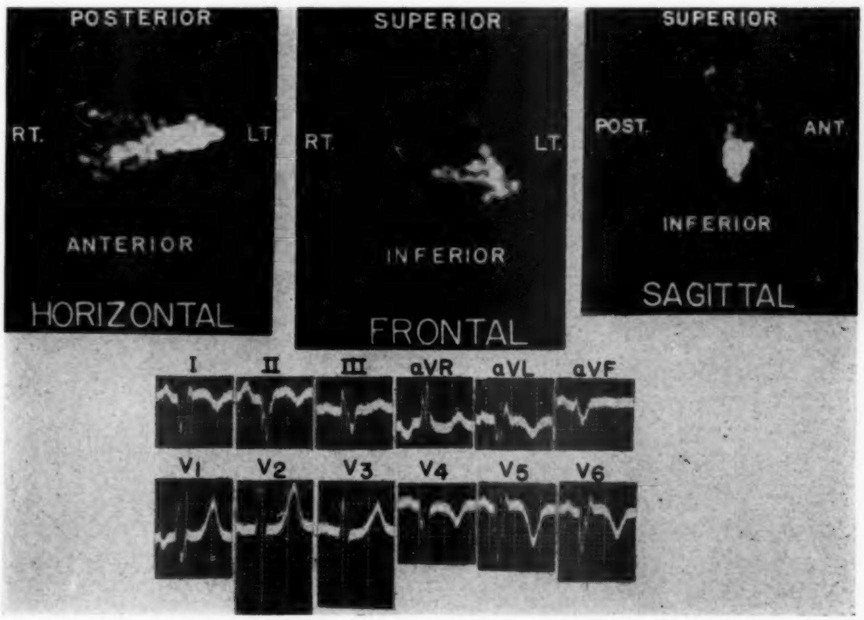

Fig. 2.—Patient W.H. with posterolateral infarction. The vectorcardiogram is in the right superior anterior octant. See text.

MATERIAL, METHOD, AND RESULTS

Five male patients, ranging in age from thirty-nine to fifty-nine years, were chosen from the wards. Each had had clinical evidence of myocardial infarction and confirmatory electrocardiograms and laboratory data. These patients were selected because they had prominent R waves in the right-sided leads.

Vectorcardiograms were taken using the method of Duchosal and Sulzer,[10] with lead placement and polarity as modified by Grishman and Scherlis.[8] The vector loop was interrupted four hundred times per second by a frequency modulator. The records of R.J.L. and P.F. (Figs. 3 and 5) were taken on another oscilloscope in which the modulator produced teardrop-shaped segments to facilitate the identification of the direction of rotation of the loop. The direction in the other cases was determined visually by three independent observers. Electrocardiograms were taken with both direct-writing and string galvanometer instruments at normal speeds on the same day as the vectorcardiograms on all patients.

The following is a pertinent summary of the five patients studied.

H.M.—A 56-year-old white male with a history of posterior myocardial infarction in 1936 and chronic alcoholism since then developed signs and symptoms of congestive heart failure in 1945. He was treated with digitalis, sodium restriction, and diuretics which maintained cardiac compensation until 1952. The electrocardiogram of July 21, 1950 (Fig. 1, A) showed the old posterior myocardial infarct and a recent anteroseptal infarct and digitalis effect. More recent posterior infarction was noted on subsequent electrocardiograms, and on Oct. 17, 1952 prominent R waves were present in Leads V_1 to V_4 and aV_R (Fig. 1B).

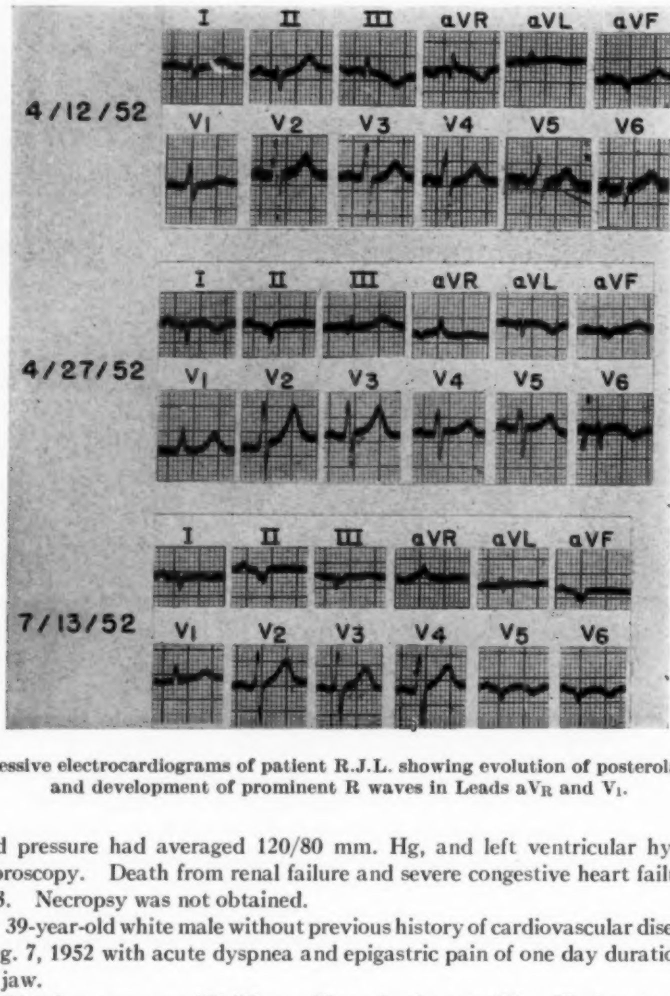

Fig. 3A.—Successive electrocardiograms of patient R.J.L. showing evolution of posterolateral infarction and development of prominent R waves in Leads aV_R and V_1.

The blood pressure had averaged 120/80 mm. Hg, and left ventricular hypertrophy was present on fluoroscopy. Death from renal failure and severe congestive heart failure occurred in February, 1953. Necropsy was not obtained.

W.H.—A 39-year-old white male without previous history of cardiovascular disease entered the hospital on Aug. 7, 1952 with acute dyspnea and epigastric pain of one day duration, radiating to the arms and jaw.

Admission blood pressure was 120/80 mm. Hg and pulse rate 120. The heart was not enlarged nor were there any murmurs or irregularities. The remainder of the physical examination was essentially negative. Recovery was uneventful. Electrocardiograms taken following admission revealed serial changes of a posterolateral myocardial infarction with prominent R wave in Lead V_1, and the QRS complex in lead aV_R consisting solely of an R wave. The electrocardiogram and vectorcardiogram taken Oct. 22, 1952 are shown in Fig. 2.

R. J. L.—A 53-year-old white male without previous history of cardiovascular disease was hospitalized in April, 1952, for an acute onset of severe substernal pain of several hours' duration.

On admission to the hospital he had a temperature of 99.2° F. orally, with a pulse rate 100, and blood pressure 104/60 mm. Hg. The physical examination was otherwise essentially negative including the heart which revealed no irregularities, enlargement, or murmurs. The patient was treated with rest and analgesics and progressively recovered without untoward incident.

Several electrocardiographic tracings taken during the course of illness and recovery showed the evolution of a posterolateral infarct and are illustrated in Figs. 3A and 3B. They showed the progressive development of predominance of the R waves in aV_R and V_1 and loss of R waves in V_5 and V_6. The electrocardiogram and vectorcardiogram taken on Feb. 18, 1953, appear in Fig. 3B.

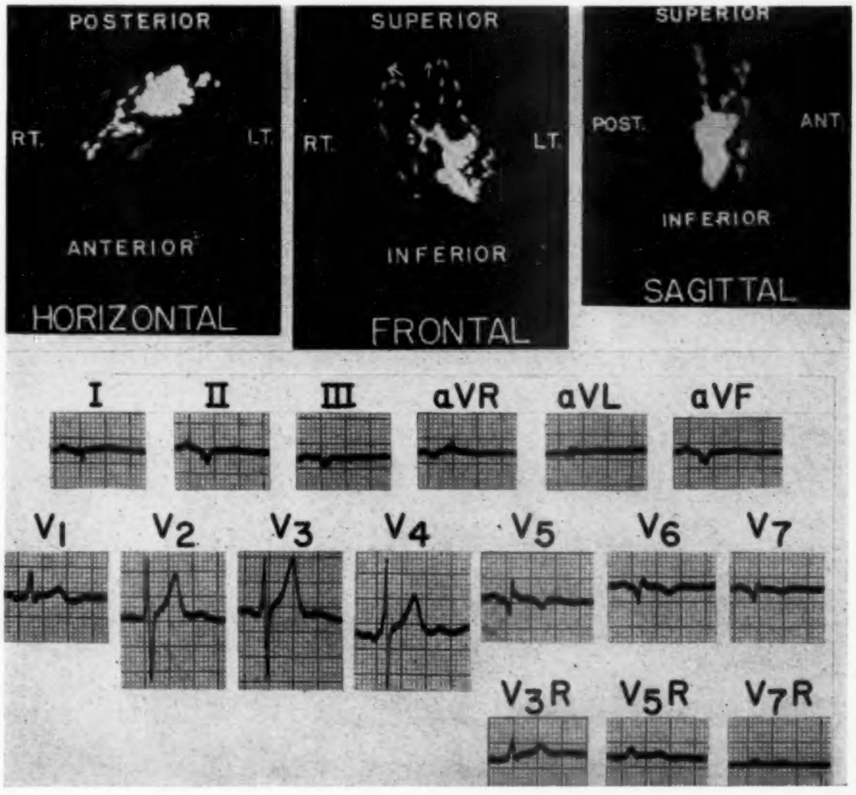

Fig. 3B.—Patient R.J.L. studied on Feb. 18, 1953. The electrocardiogram resembles the tracing of July 13, 1952 (Fig. 3A). The vectorcardiogram is in the right superior anterior octant. See text.

H. G.—A 54-year-old white male with previous history of alcoholism and hypertension, but no previous myocardial infarcts, entered the hospital on Oct. 14, 1952 with sudden onset of epigastric pain associated with dyspnea of one day duration.

Physical examination on admission was essentially negative except for a blood pressure of 140/100 mm. Hg. There were no cardiac enlargement, irregularities, or murmurs. Recovery was uneventful. Electrocardiograms taken during the course of hospitalization revealed serial changes of acute anterolateral myocardial infarction. The electrocardiogram and vectorcardiogram taken on Oct. 30, 1952 are illustrated in Fig. 4.

P. F.—A 59-year-old white male had four episodes of myocardial infarctions between March, 1941 and May, 1952. The last one was complicated by severe congestive failure with distended neck veins and pulmonary edema. The blood pressure was 130/70 mm. Hg. There was a diastolic gallop rhythm, and both the heart and liver were enlarged. There was no peripheral edema.

Old anterolateral myocardial infarction with prominent R waves in Lead aV_R was evident on electrocardiograms taken during this latter illness.

Since treatment consisting of digitalis, sodium restriction, and diuretics did not improve the congestive heart failure, radioactive iodine was administered from May, 1952, to July, 1952. This caused marked improvement in the state of compensation which has been maintained to date. The electrocardiogram and vectorcardiogram taken Feb. 8, 1953 appear in Fig. 5.

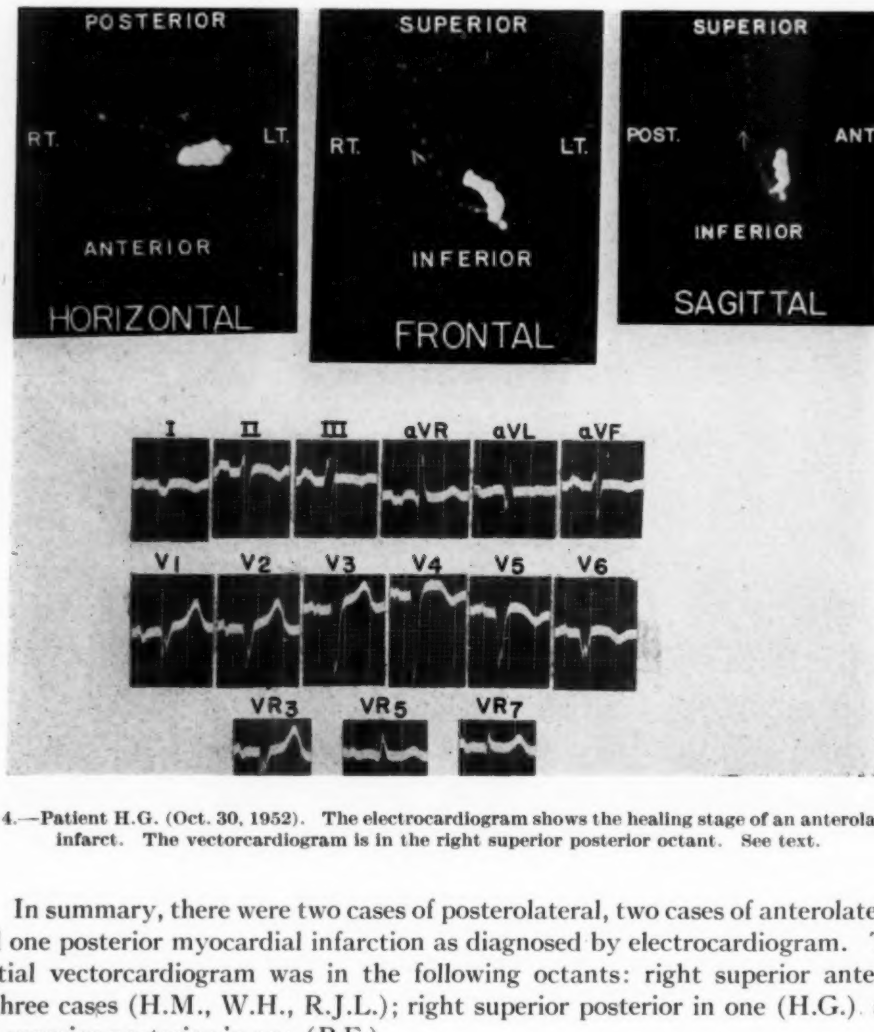

Fig. 4.—Patient H.G. (Oct. 30, 1952). The electrocardiogram shows the healing stage of an anterolateral infarct. The vectorcardiogram is in the right superior posterior octant. See text.

In summary, there were two cases of posterolateral, two cases of anterolateral, and one posterior myocardial infarction as diagnosed by electrocardiogram. The spatial vectorcardiogram was in the following octants: right superior anterior in three cases (H.M., W.H., R.J.L.); right superior posterior in one (H.G.) and left superior posterior in one (P.F.).

DISCUSSION

The anterior position of the QRS vector loop in the horizontal plane and the superior position in the frontal plane explain the tall upright R waves in Leads V_1 and aV_R, respectively, in H.M., W.H., and R.J.L. The most anterior displacement of the vector loops in the five patients studied was seen in H.M. (Fig. 1),

and accordingly tall R waves occurred in Leads V_1 to V_4. In this patient, the initial portion of the horizontal plane loop is directed slightly to the right causing the small Q waves in Leads V_1 to V_4 followed by a leftward direction of the loop producing the R waves in V_5 and V_6 (Fig. 1). In patients R.J.L., H.G., and W.H. all of the horizontal plane vector loops are directed away from Leads V_5 and V_6 so that deep Q waves occur in these leads. The most posterior displacement of the horizontal plane vector loop occurred in the tracings of H.G. (Fig. 4).

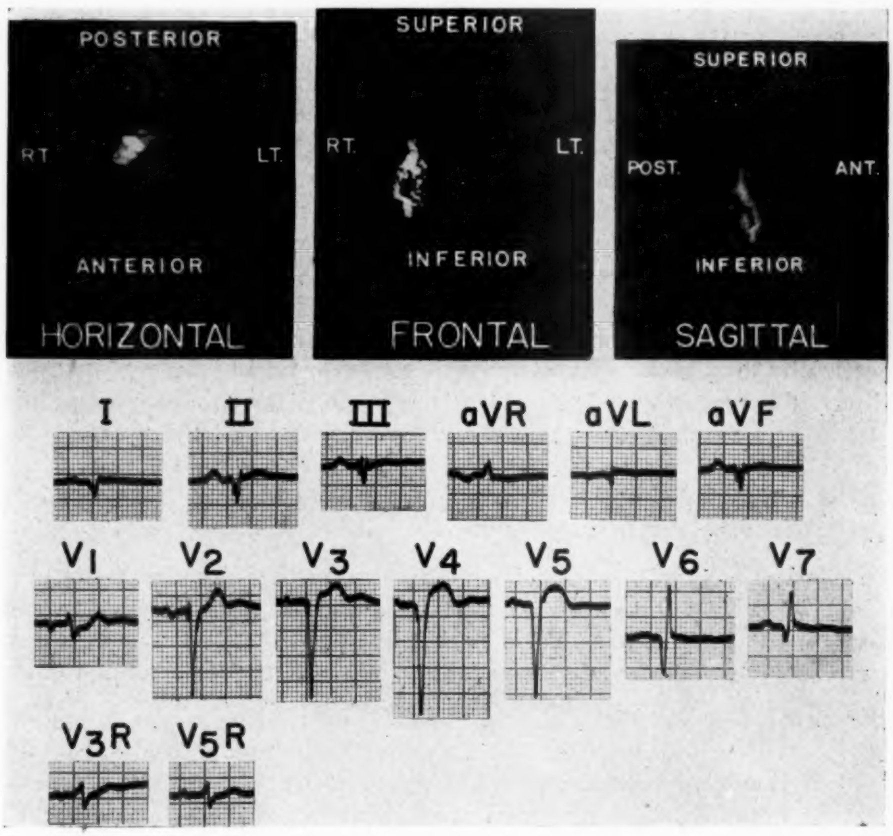

Fig. 5.—Patient P.F. with old anterolateral and recent posterior infarction. The R wave is prominent in Lead aV_R but not V_1. The vectorcardiogram is in the left superior posterior octant. See text. (Horizontal and frontal planes are clockwise, sagittal plane is counterclockwise.)

In this patient, the right posterior location of the horizontal plane vector loop explains the tiny (almost absent) R waves in V_1 and the presence of R waves in V_{R5} and V_{R7}. This right posterior displacement likewise explains the tiny R waves in Leads V_1 to V_4 and the deep Q waves in Leads V_5 and V_6. In P.F., the initial portion of the horizontal vector loop is directed to the right and clockwise, which is abnormal, resulting in R waves in V_1, V_{3R}, and V_{5R} and deep Q waves in Leads V_3 to V_6. The twisting and irregularity of the vector loops in the frontal

plane in all patients except H.G. explain the presence of the splintered or polyphasic QRS complexes in Leads aV_R and aV_L. By contrast, the frontal plane vector loop in patient H.G. is smooth and regular and qR complexes occur in Leads aV_R and aV_L.

From the electrocardiographic standpoint, patients W.H., R.J.L. and H G. exemplify the pattern described by Tulloch.[2] Electrocardiographic evidence of ventricular aneurysm was not present although tall R waves in aV_R were noted in three patients of Myers and associates.[3] However, none of the five cases herein reported had the usual electrocardiographic features of ventricular aneurysm and the latter was absent on cardiac fluoroscopy.

Patient H.M. (Fig. 1) deserves further comment. The width of the QRS complex in the precordial leads is 0.12 sec., and the electrocardiogram might be interpreted as an unusual and atypical right bundle branch block. Goldberger[9] has illustrated an electrocardiogram similar to that of H.M. and explained it tentatively on the basis of extreme clockwise rotation of the heart. There is evidence against this in the vectorcardiogram. In the horizontal plane the vector loop is usually counterclockwise, whereas in H.M. it is clockwise. In right bundle branch block observed by Grishman and Scherlis[8] and Elek and associates,[11] the block occurs in the terminal portion of the vector loop. Visual inspection by the present authors of the vector loops did not disclose any "bunching," and the suggestion of "bunching" in Fig. 1 is due to the twisting of the vector loops. Furthermore, the abnormal ventricular activation time in Lead V_6 is explicable neither on the basis of right bundle branch block nor extreme clockwise rotation. This patient illustrates the difficulties of relying on electrocardiographic interpretation alone.

Levy and associates[1] and Tulloch[2] have stated that prominent R waves in Leads aV_R and/or V_1 usually occur in posterior or posterolateral myocardial infarction; the same implication is present in the patients of Myers and associates. Since most of the left ventricle is posterior in both normal and left ventricular hypertrophy hearts, infarction in this region causes a considerable loss of electromotive force.

There is evidence that prominent R waves in right-sided leads occur usually in infarcts not only of specific location, i.e., posterolateral, but also of large size in ratio to the remaining left ventricular myocardium. Such evidence was found by examining the anatomic description of the necropsied infarcts and the published radioautographs contained in the studies of Myers and co-workers[3-6] on anterolateral and posterolateral myocardial infarction. Thus an R wave in V_1 and aV_R did not appear when there was an infarct involving the same area but of less proportional extent than the infarct in which the prominent R wave did not appear. Three of Tulloch's[2] four necropsy cases had both left ventricular hypertrophy and large posterolateral infarcts, one of which measured five by seven centimeters. The infarcted area, however, was small in relation to the noninfarcted left ventricle and in these cases prominent R waves were not present.

Two of our cases particularly well illustrate these findings and can be interpreted on the basis of size of the infarct relative to the left ventricular mass. On Aug. 21, 1950 (Fig. 1A), patient H.M. had an acute posterior myocardial infarct without prominent R waves in Leads aV_R or V_1. Two years later another apparently large posterior wall infarct increased the size of the infarcted area in ratio to the remaining myocardium, thereby producing the tall R waves in these leads. In patient P.F. (Fig. 5) the infarct resulted in a new spatial vector located more superiorly and posteriorly, and somewhat to the right, than normal but it was apparently not large enough to shift the vector predominantly to the right side.

Myers and associates[3-6] and Goldberger[9] have explained these electrocardiographic findings on the basis of anatomic rotation of the heart. By contrast, Levy and associates,[1] Tulloch,[2] and Grishman and Scherlis[8] have offered the explanation that the absence of opposing electrical forces due to the infarcted left ventricle produces the tall R waves.

The vectorcardiograms of four of the five patients reported herein clearly show that the vector loop is in the right superior octant. This can be explained by changes in the electrical field without invoking actual anatomic or "electrical" rotation. Bayley[12] has indicated that besides the unopposed electromotive force of the area diametrically opposite an area of infarction, there is also an additional electromotive force derived from the area in or immediately around the infarct which augments the potential of the uninfarcted area. Theretofore, two explanations are offered for the location of the spatial vectorcardiogram in the right superior octant in four of the five patients herein reported: (1) The loss of electrical potential from the infarcted left ventricular wall "passively" allowing the right ventricular vectors to predominate, and/or (2) A new abnormal vector is developed in the region of the infarcted left ventricle, pointing in a direction more towards the right ventricle than the left ventricle. The latter abnormal vector "actively" summates with the normal right ventricular vector producing a new and augmented vector directed towards the right.

Although cardiac rotation cannot be excluded as an explanation for the prominent R waves, a simpler explanation is available from the spatial vectorcardiogram which demonstrates new and altered vector forces resulting from myocardial infarction.

SUMMARY

1. Five patients with myocardial infarction and prominent or tall R waves in Leads aV_R and/or V_1 are reported.

2. Vectorcardiographic studies revealed that the spatial vector loop was in the right superior anterior octant in three patients, right superior posterior octant in the fourth patient, and left superior posterior octant in the fifth patient. The horizontal plane vector loop was strikingly displaced to the right in four of the five patients.

3. The development of tall R waves in Leads aV_R and V_1 is shown in two patients.

4. Evidence is presented that these prominent R waves occur in either antero- or posterolateral wall myocardial infarction and that the infarct must be large in ratio to the remaining myocardium.

5. The spatial vectorcardiogram clearly explains the reason for the prominent R waves and the concept of cardiac rotation need not be involved.

We are indebted to Mr. Peter Pasquinelli of Yuma, Arizona, Mr. Joseph Levy of Dayton, Ohio, and Mr. Solomon Rosenthal of Los Angeles, Calif., and an anonymous donor for financial assistance and Mrs. Janet Y. Camlin for her able collaboration.

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THE INFLUENCE OF KHELLIN (VISAMMIN) UPON THE ELECTROCARDIOGRAM

IGNACY PINES, M.D.

CARACAS, VENEZUELA

THE modern history of the plant (*Ammi visnaga*)* and of substances which can be extracted from it started after it had been shown that khellin produces the relaxation of smooth muscles through a direct action on muscular fibers and that this property can be of value in the treatment of human diseases of spasmodic character or origin.

The action of khellin in man was studied particularly in respect to its influence upon the coronary circulation. During the last six years numerous papers and studies have appeared dealing with the treatment of coronary disease by khellin. The majority of them are favorable and some frankly enthusiastic, with the exception perhaps of the paper of Greiner and associates.[1] These authors concluded that the effects of a tablet of khellin are hardly superior to a tablet of lactose administered as a placebo. Nevertheless, many authors have been able to show the beneficial effects of khellin upon the course of angina pectoris. Some others have supported this relief by electrocardiographic examinations with the exercise test and some without it. Similarly, the electrocardiographic changes, obtained during cardiac anoxia induced by breathing of mixtures poor in oxygen or after the injections of ergonovine maleate, have shown marked improvement if khellin has been administered for long periods of time.

Further, khellin has been found to be a more efficient coronary vasodilator than the xanthine derivatives, and its influence, although not so instantaneous as that of nitroglycerine or amyl nitrite, was more persistent. Moreover, khellin did not induce a greater fall of blood pressure or would not be responsible for a secondary coronary insufficiency. This is obviously a great disadvantage of nitrates, as recently pointed out by Contro and associates.[2] The new antispasmodic drug, dioxyline phosphate, cannot be considered, from the point of view of coronary vasodilatation, as superior to khellin (Best and Coe).[3]

To some extent the selective vasodilator action of khellin on the coronary arteries has been confirmed in experiments carried out on animals. These studies have been performed on a variety of intact animals. Some authors have used the isolated heart and others the Starling heart-lung preparation. In general,

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From the Institute of Veterinary Investigations in Caracas, Venezuela.

This study was partially presented in Rio de Janeiro and in São Paulo in the month of October, 1952, on invitation of the Brazilian National Council of Scientific Research.

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*In spite of the growing clinical interest focused on the drugs obtainable from the seeds of the plant called *Ammi visnaga*, the pharmacologic properties of these drugs and most particularly those of their principal component known under the name of khellin or Visammin have not been definitely established.

all these experiments gave approximately similar results to the extent that the action of moderate doses of khellin was found to increase the coronary blood flow, which was some times estimated as being four times greater than the effect induced by the administration of aminophylline.

However, the experimental studies to determine the influence of khellin upon cardiac fiber and the arterial blood pressure have not been so numerous, and their results have led to differing conclusions. In 1932, Samaan[4] established that the rapid intravenous injection of a considerable amount of khellin caused a pronounced reduction of the arterial blood pressure. According to the same author the descent of blood pressure was due in part to direct action of the drug upon the heart muscle and, to a lesser extent, to stimulation of the vagus. Consequently, the administration of atropine or section of the vagus lessened, according to Samaan,[4] the effect of khellin upon the blood pressure. The connection between the blood pressure fall and the direct response of heart muscle, on the other hand, was demonstrated by the fact that the drug had always definite chrono- and inotropic effects upon the heart, regardless of whether the experiments were carried out on an isolated heart, on the Starling heart-lung preparation, or on the intact animal. The administration of khellin in all of these experiments was a depression of the frequency and the amplitude of heart beats. In experiments with perfusion of the hearts of toads, stronger solutions could produce total arrest of cardiac activity.

The influence of khellin in lowering blood pressure was also an object of recent studies by Lian and Charlier.[5] The hypotension after the administration of khellin has been described as . . . "immediate, strong but of a very short duration." This fall of blood pressure was evident if khellin was administered after some constrictive drugs, like Adrenalin or Pituitrin, or during the period of hypertension produced by severance of both nerves of Hering and Cyon. Finally, khellin could abolish the vascular response to pressure on the carotid sinus and also the fall of blood pressure as a consequence of occlusion of the common carotid arteries on both sides.

Although there were no comments in regard to the negative influence of khellin upon chrono- and inotropic qualities of heart muscle, postulated by Samaan,[4] the French authors felt justified in explaining the protective activity of the drug on the ventricular fibrillation caused by the combination of Adrenalin and chloroform, by some antifibrillatory properties of khellin consisting essentially in the diminution of cardiac excitability.

Conversely, Anrep and his co-workers[6] estimated in a different way the influence of khellin upon the heart muscle, and consequently also upon the arterial blood pressure. They affirm that the inotropic negative activity of khellin comes to the fore, exclusively in isolated hearts perfused with an excessively strong concentration of khellin. Those responses according to the same authors have never been observed on heart-lung preparations. In regard to whole animals, it was true enough that a rapid intravenous injection of a dose of 30 mg. could produce in a dog a pressure fall of some 50 mm. and a slowing of the heart. Such a reaction, however, lasted only one or two minutes, when the blood pressure, the heart rate and respiration returned to normal. Moreover, the intra-

venous injection of 250 mg. in a dog weighing 12 kilograms did not produce any evident electrocardiographic alterations (Anrep and associates[7]).

METHOD

The present work is an electrocardiographic study of the alterations produced by khellin injections in animals. Endoelectrograms of the highest third part of the right atrium were nearly always used. Since the pioneer studies on animals by De Mayer,[8] the endoelectrograms at different levels of cardiac cavities are quite well known under physiologic and some pathologic conditions. Until now the intracavitary electrogram has not been applied frequently to pharmacologic studies. However, one of the fundamental properties of heart muscle, i.e., conductivity, requires a separate consideration of changes which can affect selectively the conductive system and the ordinary heart fiber, or both of them simultaneously. Nevertheless, as it appears, the majority of authors, in order to observe the electrocardiographic alterations produced by some drugs, have limited themselves to the use of the standard or, in other cases, of unipolar extremity and precordial leads.

These investigations have been carried out on 5 horses of different size, 25 young bulls of approximately 50 kilograms in weight, and 5 dogs of approximately 15 kilograms body weight.* The endoelectrograms from the highest third part of the right atrium were very similar if not identical in all of these three species. Thus, when the catheter tip was close to the sinoauricular node, the auricular complex was uniphasic and entirely below the isoelectric line. When, however, the exploring electrode was below the sinoauricular node, we had to deal with a triphasic auricular complex beginning with a distinct negative deflection, sometimes called Q_a wave. The ventricular complex in all our experiments was of qR or QR type. The S-T segment was below or in the isoelectric line, the T wave was negative and nearly V shaped in the bulls and dogs, and diphasic—plus minus—type in the horses.

All animals, except dogs, were lying on their left or right sides on a wooden base, which served as an electric insulator. In all cases the experiments were carried out under general anesthesia induced by the intravenous injection of adequate quantities of a 20 per cent solution of chloral hydrate. The standard and unipolar extremity leads were then taken by means of big needles introduced under the skin. In all unipolar leads the central terminal of Wilson was used as a point of reference. Once the standard and unipolar leads of the extremities and sometimes of the precordium were obtained, we introduced through the external jugular vein a well-insulated cable to the end of which had been soldered a small copper ball of approximately 3 mm. in diameter. This ball was passed inside the right atrium, and its location was established electrocardiographically, so that once the uniphasic or triphasic auricular complex typical for the upper parts of

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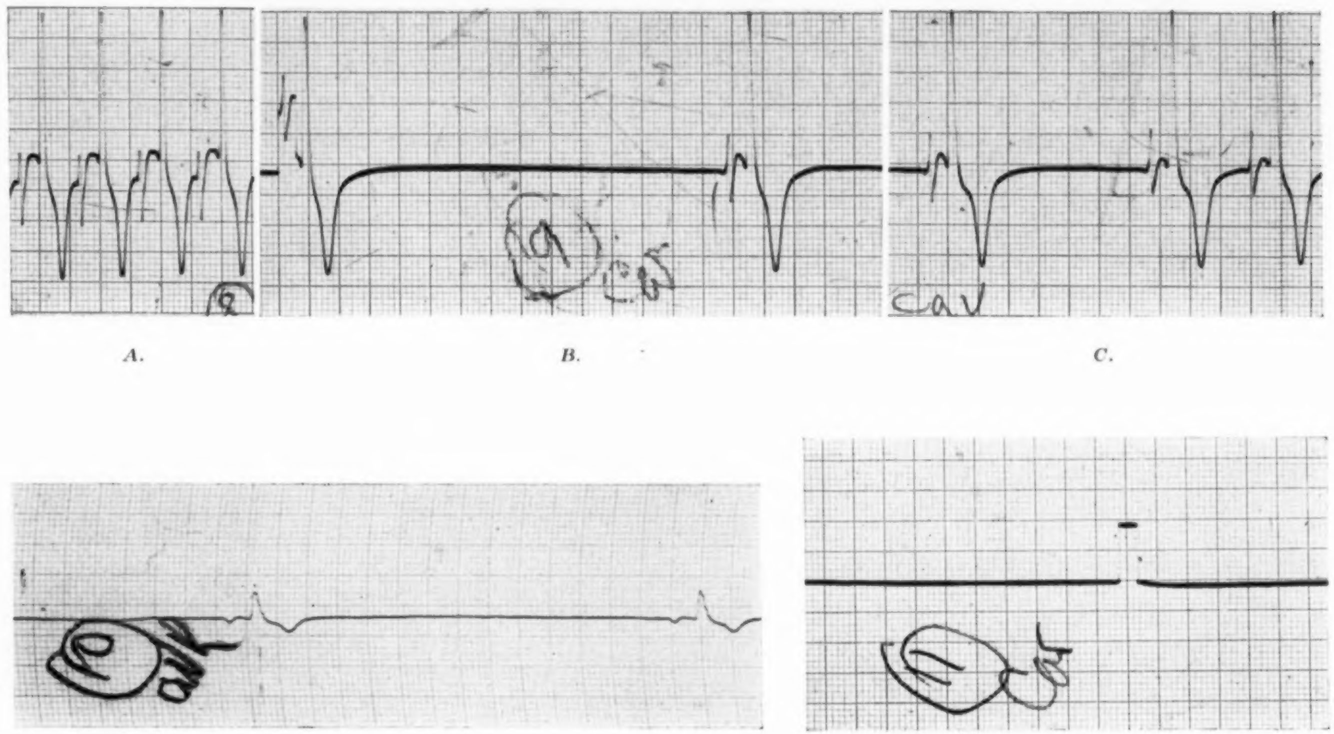
*The reason we used big mammals in the majority of our experiments was to enable us to make some physiologic observations which will be presented in detail elsewhere. The animals were put at our disposal by the Ministry of Agriculture and Dairy Cattle.



A. B. C.

D. E.

Fig. 1.—*A*, Right auricular endoelectrogram of bull before khellin. *B*, The same lead during and after rapid intravenous injection of 7.36 mg. of khellin per kilogram of body weight. *C*, The same lead a few seconds later; slight recovery. *D*, aV_R of the same bull, a few seconds after *C*. *E*, Complete arrest of auricles and ventricles.

the right atrium was obtained, the cable was fixed by a hemostat to the wall of the dissected vein. The same hemostat also fixed a large needle through which various drugs were injected. In some experiments khellin only was used; in others there were injected before or after khellin, digitalis, ouabain, paratropine, mercurial diuretics, dioxyline (Paveril) phosphate and methylene blue.*

As soon as ventricular fibrillation appeared or the heart stopped altogether, we proceeded to open the chest of the animal in order to determine the exact location of the endoelectrode in the right atrium. In the 5 experiments on dogs, the same type of anesthesia was used. Artificial respiration was instituted after opening the chests of the animals. The pericardial sac was also opened by the broad triangular incision and its borders fixed to the chest walls. The disturbances of the heart action were observed directly and registered by means of an endoelectrogram led from the upper part of the right atrium. In this group of experiments khellin only was administered.

EXPERIMENTS

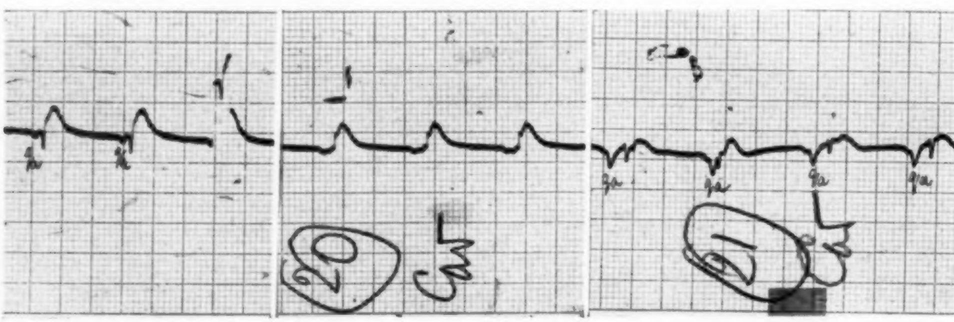
The experiments on bulls will be described first, as these were more numerous than the experiments performed on horses or dogs. In summarizing the results it should perhaps be stated that the khellin was administered rapidly and in quantities from 5 to 10 mg. per kilogram and produced alterations in the three fundamental properties of heart muscle, i.e., in its chronotrophic, dromotrophic, and bathmotropic functions. Thus, almost simultaneously with the intravenous injection, even before the syringe attached to the needle could be withdrawn, there appeared a considerable fall of heart rate to a level of ½, ⅓, and rarely, ⅕, of that before the administration of the drug. This reduction in rate was sometimes progressive, so that after a few minutes the heart activity ceased completely. In other experiments, however, the same reduction of heart rate developed in two well-defined phases, i.e., a few seconds after the injection of khellin the automatic function of the sinoauricular node recovered a little, only to diminish again in a short time. Simultaneously with this postkhellinic bradycardia there appeared frequent disturbances of intraauricular, auriculoventricular, and intraventricular conduction. Five times the disturbance of auriculoventricular conduction was a complete auriculoventricular block, and a few seconds later there was a complete arrest of ventricular activity, so that the auricles only continued beating. This phenomenon occurred particularly if khellin was administered after digitalis, which will be described in detail.

Experiment 59† illustrates the influence of khellin when administered by rapid intravenous injection upon the heart of a bull (Fig. 1). In this experiment there is recorded a typical pattern of the higher part of the right atrial lead, with a sinus rhythm of the frequency of 154 per minute; a diphasic auricular complex which started from a not very clear q_a and consisted in a R_a of 4 mm. of amplitude and S_a of 7 mm. of amplitude. This complex also lasted 0.075 sec. and the delay of auricular intrinsic deflection was 0.04 sec., counting in the same endoelectrogram from the beginning of the auricular complex. The initial part of the ventricular complex, on the other hand, lasted 0.075 sec., and the pattern of ventricular QRS was qR; S-T was sagging obliquely and T was

*We are indebted for the supply of these drugs to the following firms: C. A. Laboratorio Farmacologico Venezolano for Vis-Kelin, Industrial Farmaceutica de Levante for Kelicorin, Baute & van den Bussche for Khellin Delalande, Pauly Sus Hijos & Cia for Digitaline Nativelle and Ouabaine Arnaud, Dr. Lazaro-Buenos Aires for Paratropine, and Eli Lilly & Company, Indianapolis, Ind., for Dioxyline Phosphate.

†These experiments form a part of a much more extensive work; therefore, the numbering of the experiments was not necessarily made from the point of view of the present study.

negative and had an amplitude of 17 mm. Immediately after the rapid injection of 500 mg. of khellin into the external jugular (i.e., 7.36 mg. per kilogram) there appeared a sinus rhythm with a frequency of 21 to 28 per minute only. The initial q_a wave was much more clearly seen, lasting 0.02 sec. instead of 0.01 sec., the duration of the auricular complex was 0.10 sec. The delay of instrinsic deflection was 0.06 sec., the amplitude of R_a was 6.5 mm., and that of S_a was 3.5 mm. According to Sodi-Pallares,[10] these three signs, i.e., increase of the positivity, reduction of the negativity, and an increase of the delay of intrinsic deflection, constitute in the case of the auricular complex, the triad of the lesion. In the same experiment, although the P-R interval did not show much alteration, we could record some changes of the ventricular complex. These consisted principally in an increase of the duration of the initial part of the ventricular complex from the original 0.075 sec. up to 0.10 sec. In accordance with the study of Alfredson and Sykes,[11] however, an increase of the duration of the QRS of about 0.025 sec. is more than sufficient in a heart endowed with such an efficient conductive system as is the heart of dairy cattle, to warrant a diagnosis of a disturbance of conduction in one of the branches of the bundle of His. Some 12 sec. after all these changes mentioned above, the sinoauricular node recovered to such an extent that the heart rate increased again to 115 per minute, but a little later both the auricles and the ventricles were arrested.

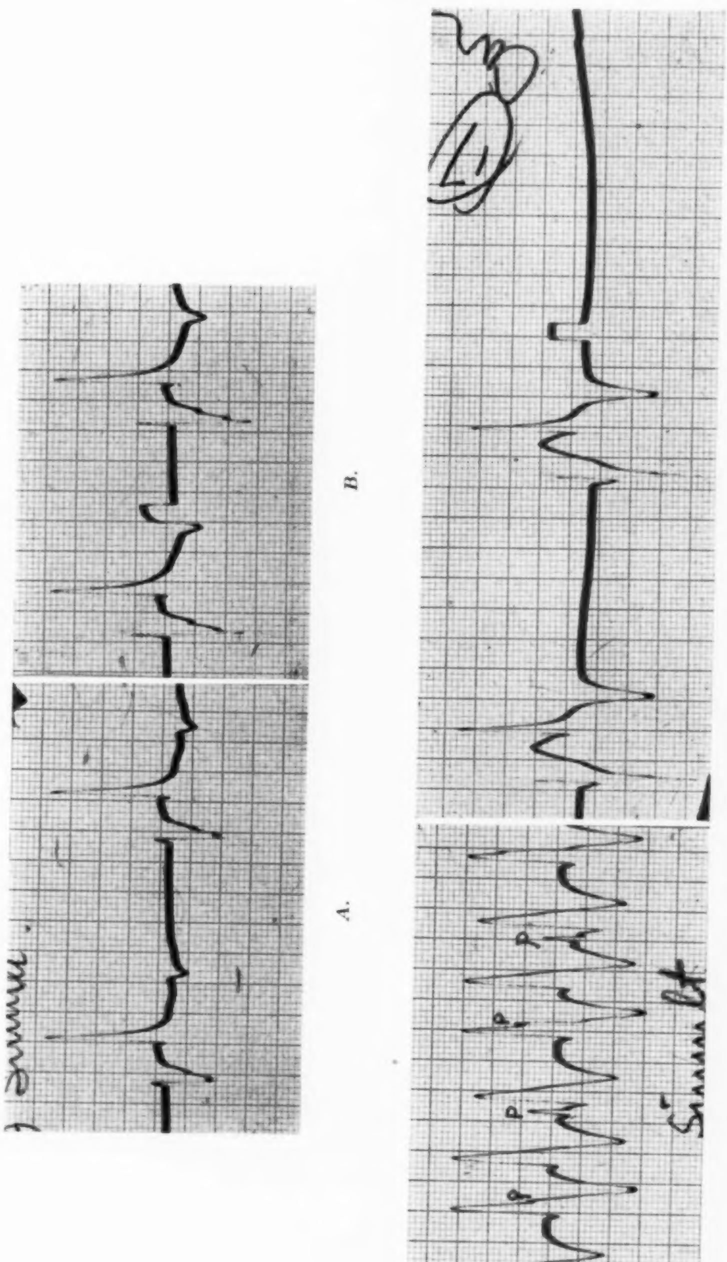


A. *B.* *C.*

Fig. 2.—*A*, Right auricular endoelectrogram of a bull after intravenous administration of 19.73 mg. of khellin per kilogram of body weight; only auricles are beating. *B*, Intra-auricular block. *C*, The Q_a wave is now clearly separated from the main auricular complex.

Other experiments on bulls with rapid intravenous injections of khellin gave similar results, but because of physiologic considerations Experiment 78 is recorded (Fig. 2). In this experiment, after the final injection of khellin we had to deal with a complete ventricular standstill. After a few isolated auricular beats, the auricular complex was much wider, acquiring to some extent an aspect similar to ventricular complexes in bundle branch block. Later, the intra-auricular conduction seemed to recover. However, the initial q_a wave which a little before was melted with the R_a now separated itself from the main part of the auricular complex. The duration of this wave was still 0.06 sec.; the interval q_a R_a was now 0.13 sec.; the interval from the end of q_a up to beginning of R_a measured 0.07 sec. In our opinion there is a possibility that the curve described could be a graphic record of incomplete sinoauricular block.

With the bradycardic heart of horses the results were not so uniform, as can be seen from the example of Experiment 20 (Fig. 3). Here, after the khellin administration in a very small dose of 2 mg. per kilogram, the initial frequency increased up to 63 per minute. Two minutes later, however, there started a ventricular tachycardia with a frequency between 136 and 176 per minute, the auricles beating with a frequency of 103 per minute, as can be clearly seen from the endoelectrogram in which the auricular deflections are easily identifiable. Finally, one minute later the sinoauricular rhythm again makes its appearance with a frequency of around 25 per minute, with a neat q_a wave and with a monophasic deformation of the auricular complex, both of which did not exist before the administration of khellin.

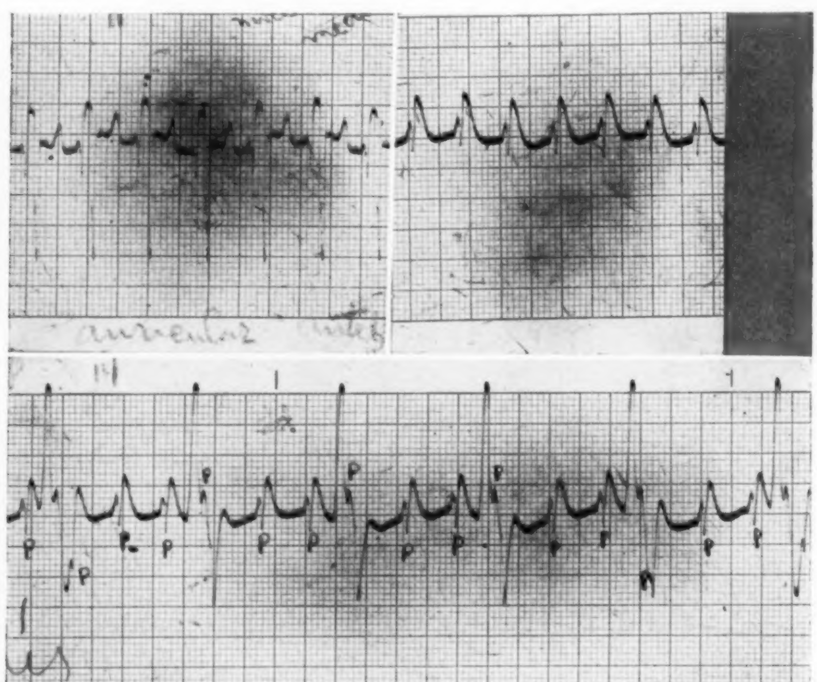


A. B. C. D.

Fig. 3.—*A*, Right auricular endoelectrogram of a horse before khellin. *B*, The same lead after rapid intravenous injection of 2 mg. of khellin per kilogram of body weight. *C*, Few seconds after *B*: ventricular paroxysmal tachycardia. *D*, Sinus bradycardia. (N/2): Electrocardiograph is standardized so that 1 mv. is causing a deflection of 5 mm. (one-half normal = N/2).

The experiments on dogs, although there were five of them only, have amply confirmed the results of the experiments on small bulls. These results, if one draws a comparison between one and another experiment, differed perhaps a little more than on bulls in respect to dosages or order of appearance of disturbances. Thus, in Experiment 1, after the initial dose of 13 mg. per kilogram the pattern of auricular and ventricular complexes as well as auriculoventricular conduction time showed slight changes only. The initial sinus rhythm was preserved, although the frequency of 130 per minute was reduced to 125 per minute. However, the situation was completely different as soon as the next administration of the same quantity of drug took place. First, the duration of auricular complex started slowly to increase from the original figure of 0.06 sec. to 0.08. Then there was recorded a progressive alteration of the initial part of the ventricular complexes together with an increase of its duration and an augmented delay of the intrinsic deflection. Finally, the partial auriculoventricular block 6:1 made its appearance, and soon thereafter a complete auriculoventricular block and total arrest of the ventricles.

A. *B.*



C.

Fig. 4.—*A*, Right auricular endoelectrogram of dog. *B*, The same lead a few seconds after the rapid intravenous administration of 18 mg. of khellin per kilogram of body weight; ventricular arrest. *C*, 2 minutes later; auricular tachycardia with block (N/2).

The results of another experiment (Fig. 4) deserve special mention. The initial frequency was 158 per minute. We were leading the electrogram from the mid-level of the right atrium, and therefore the auricular complex had a pattern of rSr.′ A few seconds after the administration of 18 mg. of khellin per kilogram the auricular frequency increased up to 200 per minute and the ventricles stopped beating altogether. A little later there was an access of paroxysmal auricular tachycardia with block, very similar to the condition recently analyzed by Lown and associates.[12] The auricular frequency was 176 per minute, whereas that of the ventricles was 62 per minute. The ventricular complexes were of a bundle branch block pattern.

Khellin plus Paratropine.—The results of Experiment 71 are quite interesting. After the injection of 300 mg. of khellin into a bull which received previously 60 mg. of Paratropine (Dr.

Lazaro, Buenos Aires), we have observed a very slight reduction of frequency to a level of 136 instead of 146, recorded in the beginning of the experiment. Simultaneously, however, one could establish a monophasic deformation of the auricular complex and a significant alteration of intraventricular conduction with the pattern of the left bundle branch block. Nevertheless, the second dose of 250 mg. of khellin produced a reduction of the frequency to the level of 42 per minute, and this maintained itself in spite of the additional administration of 60 mg. of Paratropine (the animal received a total dose of 9.64 mg. of khellin and 2.10 mg. of Paratropine per kilogram). One experiment in which both vagus nerves were cut gave similar results. The khellinic reduction of the frequency was a little less impressive than we were led to expect after the results of the experiments previously described.

Khellin plus Methylene Blue.—The methylene blue interested us considerably, because according to the results of the experiments of Heymans and Maigre,[13] Maigre and Koskowsky,[14] and of Cook,[15] this dye paralyzes the vagus nerves and inhibits the influence of acetylcholine through an action which is localized even more peripherally than that of atropine and very possibly in the heart itself. In the investigations carried out by the author[16] in 1934 one could observe that already 1 μg of acetylcholine had a distinctive inotropic negative influence, whereas after the administration of methylene blue (3^{-10} mol.) even 5 μg of acetylcholine lacked any activity.

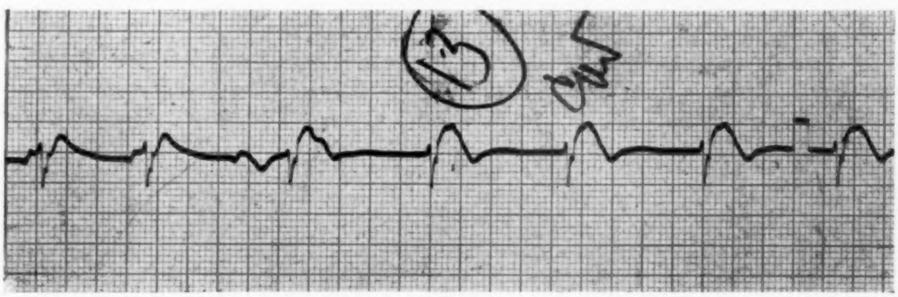


Fig. 5.—Right auricular endoelectrogram of a bull after 40 mg. of methylene blue and 6 mg. of khellin per kilogram of body weight. Ventricular arrest. Apparent separation of Q_a wave from main auricular complex and sudden drop of frequency (N/2).

In Experiment 72 we administered to a bull, 50 kilograms in weight, 40 c.c. of a five per cent solution of methylene blue (2 grams of pure dye or 40 mg. per kilogram of animal). Immediately there appeared signs of lesions of the auricular and of the ventricular myocardium. One minute later, when the heart muscle recovered a little, we injected 300 mg. of khellin (6 mg. per kilogram). The ventricles stopped at once, and the auricles only continued to beat. Fig. 5 is presented because of the interesting alterations of the auricular complex. In the beginning of the lead the auricular complex is nearly normal and appears rhythmically with a frequency of 91 per minute. Preceding every auricular complex and at a time interval of around 0.09 sec. we see a peculiar wave composed of two negative parts which are located on two different levels with reference to the isoelectric line. In proportion to the progress of inscription of this endoauricular electrogram the wave under discussion seems to separate itself more and more from the main auricular complex and finally gets completely isolated from the next or third main auricular complex. After this the wave mentioned above is nowhere to be seen, and the main auricular complex showing some alterations of its pattern begins with a simple r. Moreover, the auricular frequency slows to 66 per minute.*

Khellin plus Mercurial Diuretics.—In 1944 Pines and associates[17] showed that the intravenous injection of mercurial diuretics in a suitable dosage leads to the animal's death through ventricular

*As will be explained in a separate article ("The Origin of the Initial Negative Deflection in Right Auricular Endoelectrogram"), it seemed interesting to us to consider the possibility whether the wave in question could perhaps represent the activity of the sinoauricular node, and our tracing illustrates the sudden change of the sinus into some kind of auricular ectopic rhythm.

fibrillation. It was also found that the solution of 20 per cent of magnesium sulphate, if administered simultaneously, afforded a certain protection against the ventriculo-fibrillatory effects of mercurial diuretics. The derivatives of thiol and particularly 2,3-dimercapto-1-propanol have the same or even a little more preventive influence, as has been established by Craver and associates.[18] Since the mercurial diuretics are used as one of the principal drugs for the treatment of heart disease, we wanted to know to what extent the response to intravenous injection of mercurial diuretics would be changed after the previous administration of khellin.

During Experiment 63 there was injected into a bull weighing 60 kilograms, 250 mg. of khellin. The drug did not fail to alter the intra-auricular and intraventricular conduction as shown by the changes of respective complexes. However, when we administered intravenously three minutes later, 5 c.c. of Gortulin (0.083 c.c. per kilogram) there appeared in a question of seconds a typical left bundle branch block and a few minutes later ventricular fibrillation. It should be pointed out that the auricular complex did not show any further alteration under the influence of Gortulin, a fact which confirms the observation of Pines and associates[17] that the mercurial diuretics exert the strongest activity below the auriculoventricular node.

Other experiments with mercurial diuretics gave the same results so that perhaps it could be concluded that the khellin does not afford any protection against the ventriculo-fibrillatory influence of the mercurial diuretics.

Khellin plus Digitalis.—Experiment 75 can give some clues respecting the response of the heart to khellin if digitalis has been administered shortly before.

A bull weighing 51 kilograms was injected with 10 mg. of Digitaline Nativelle or 0.196 mg. of Digitaline per kilogram of body weight. From Levy and Cahen's[20] experiments we know that for dogs the minimal lethal dose (m.d.l.) is from 1.60 to 1.82 mg. per kilogram. The bull received, therefore, in one injection approximately one-tenth of the minimal lethal dose.

The alterations in endocardiogram are shown in Fig. 6. The heartbeats remain rhythmic; the frequency falls from 113 to 73 per minute; the initial q_a wave disappears; the duration of the initial part of the auricular complex increases by 50 per cent, whereas that of the ventricular QRS shortens in some 20 per cent and T waves are now less deep and V shaped.

As soon as the heart recovered and the q_a wave reappeared, there was injected intravenously 250 mg. of khellin, or 4.90 mg. per kilogram of animal body weight. The auricular complex this time changed very little, but the main alterations were found in the ventricular complex, which at once acquired the form of the right bundle branch block. A few seconds later terminal ventricular fibrillation started.

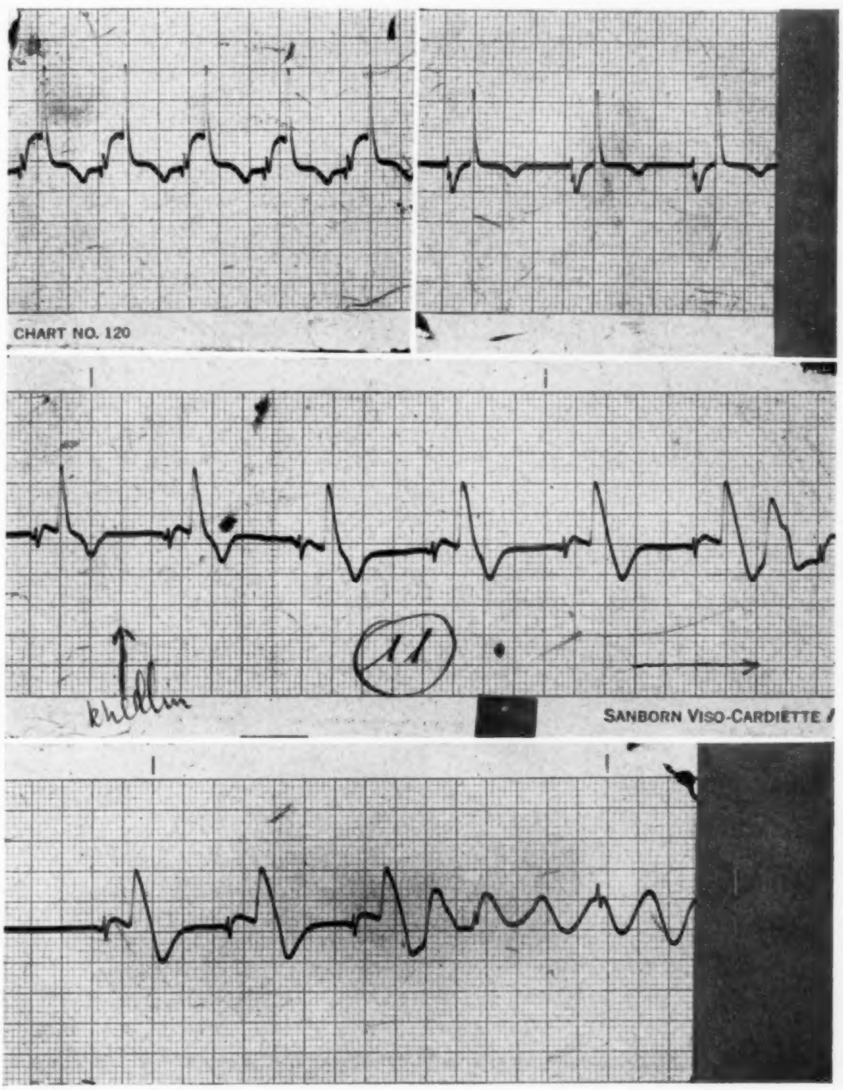
In Experiment 79 both vagi were cut in a bull weighing 77 kilogram. The initial dose of khellin was 250 mg. or 3.24 mg. per kilogram. The chronotropic effect, although perhaps a little reduced, was still clearly discernible. Three minutes later 500 mg. of khellin or 6.48 mg. per kilogram were administered. This time there were slight alterations of the auricular complex, a definite right bundle branch block, and rather insignificant prolongation of auriculoventricular conduction. A very small dose of 3.75 mg. of Digitaline injected at that moment produced final ventricular fibrillation.

During these two, as well as the other experiments with both khellin and digitalis, we have been impressed by the rather obvious summation of the effects of these two drugs upon the intraventricular and auriculoventricular conduction, as well as upon the frequency of the discharge of the stimuli by the sinoauricular node. Also, when both of the drugs were injected, the ventricular fibrillation appeared much earlier, than when these substances were administered separately.

Khellin plus Ouabain (Strophantus Gratus).—The relation of khellin to ouabain was less uniform and a little different from that of khellin to digitalis. Experiment 70 was one of seven with ouabain and khellin. The initial electrogram of a bull weighing 74 kilograms was led from the higher part of the right atrium, and consequently was distinguished by the presence of the diphasic auricular complex, in which there was a small initial q wave and a predominance of the S wave upon r, and of a ventricular complex in form of qR with a T wave negative and V shaped. The only unusual quality of this auricular endoelectrogram was a straight horizontal course of the S-T segment. After the administration of 250 mg. of khellin, i.e., 3.37 mg. per kilogram, we observed the following: the usual sinus bradycardia, the increase of the duration of auricular as well as of ventricular complexes and of P-R segment, a certain shortening of ventricular Q-T, and also a

slightly greater distinctness of q_a wave. Immediately afterwards, 20 mg. of ouabain, or 0.27 mg. per kilogram (about 2.7 cat units per kilogram) were injected. For a short time the alterations were insignificant. Then, six minutes later (in all our experiments the chief effect of ouabain comes to the fore in around 5 to 6 minutes as a rule), we could observe, successively, the monophasic auricular and ventricular waves, a very strong sinus bradycardia, a ventricular tachycardia with ventricular complexes of bundle branch block pattern, and finally ventricular fibrillation. The results of all experiments with khellin and ouabain could be summarized as follows: the khellin apparently has not a very decisive influence upon the heart's response to an intravenous injection of a solution of the *strophantus gratus*; sometimes due to khellin administration, the

A.



B.

C.

D.

Fig. 6.—*A*, Right auricular endoelectrogram of a bull. *B*, The same lead after intravenous administration of 0.196 mg. of Digitaline Nativelle per kilogram of body weight. *C* and *D*. The same lead after additional administration of 4.90 mg. of khellin per kilogram of body weight: *C* and *D* form a continuous strip.

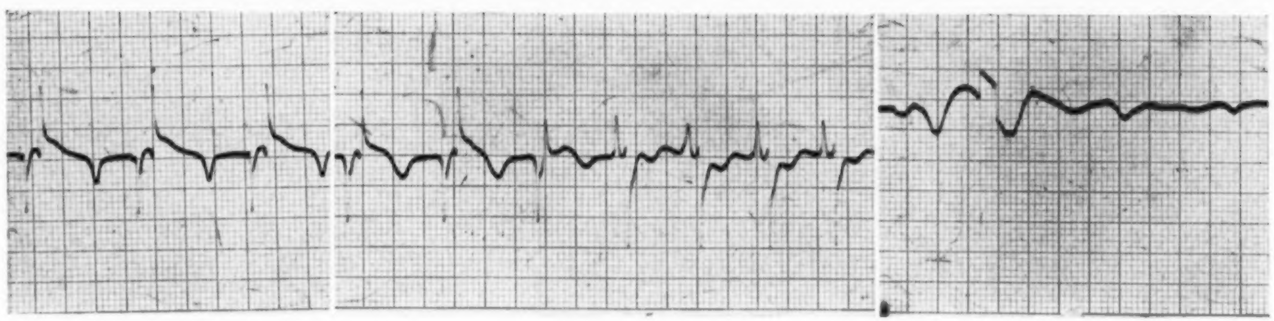


Fig. 7.—*A*, Right auricular endoelectrogram of a bull. *B*, After second administration of dioxyline phosphate; total inversion of auricular and ventricular complexes after third beat. *C*, After intravenous administration of khellin (N/2).

alterations of conduction were apparent a little earlier than we could expect on the basis of our experiments with the ouabain alone. At another time this happened rather late. The same could be said with regard to ventricular fibrillation. The khellin, therefore, does not show any protective activity against the production of ventricular fibrillation depending on the injection of ouabain.

Khellin plus Dioxyline Phosphate.—Dioxyline phosphate has been introduced recently for the treatment of angina pectoris. Some authors (Best and Coe[3]) have compared the beneficial effect of khellin and dioxyline phosphate upon patients with angina. Consequently, one could think perhaps of the association of both of these drugs for the treatment of the coronary disease. There are some experimental studies (Henderson and associates[21]), in which it has been demonstrated that the intravenous injection of 20 mg. per kilogram of dioxyline phosphate in a dog leads to an increase of heart rate, an increase of the amplitude of the P wave, diminution of the amplitude of QRS, and a total inversion of the T wave. We have devoted during this study four experiments to dioxyline phosphate and our results were somewhat different from the results and conclusions reached by other authors.

Experiment 88 could be used as an example. In the beginning of this experiment (Fig. 7, A) the auricular endoelectrogram was of the usual pattern: the auricular complex, with an initial small q wave and a small r, consisted nearly totally of a deep S wave; the ventricular complex of qR pattern with a negative and V-shaped T wave; the frequency was 88 per minute.

The intravenous injection of 320 mg. of dioxyline phosphate or 6.66 mg. per kilogram of body weight did not produce significant changes; the q_a wave lasted perhaps a little longer and the heart slowed. Conversely, further administration of 128 mg. of dioxyline phosphate (2.66 mg. per kilogram; the bull weighed 48 kilograms) produced sudden alterations. In the beginning, after the injection of the second and final dose of dioxyline phosphate the frequency increased a little (Fig. 7, B), the q_a wave and r_a wave disappeared, S_a wave was deeper, S-T segment of the ventricular complex was a little more convex and the T wave less V shaped. However, 12 sec. later there appears a total inversion of the tracing; the auricular complex becomes distinctly and exclusively positive; the ventricular QRS complex becomes completely negative (rS pattern) with the S wave amplitude exceeding that shown previously by R wave, and with diphasic T wave instead of entirely negative T in the beginning of the tracing.

The intravenous injection of 250 mg. of khellin (4.90 mg. per kilogram) at this stage produces successively the disappearance of auricular complex, the great prolongation of the ventricular QRS, and finally irreducible ventricular fibrillation (Fig. 7, C).

DISCUSSION

Analyzing the results of our experiments one can reach the following conclusions:

In the first place, these experiments have been successful to the extent that they have shown the value of auricular endoelectrograms for the pharmacologic studies of the heart. The most interesting from this point of view was the experiment with the dioxyline phosphate. Whereas other authors could observe, after the intravenous injection of the drug in question, slight changes of the amplitude of P wave, we observed the gradual development of the intra-auricular conduction disturbances. The effect was similar to the difference between the direct observation of the same event and the record registered by a slow motion camera.

In the second place, we have been able to show that khellin has a strong influence upon the heart muscle. As we have mentioned in our introductory remarks, some authors on the basis of their experiments were well aware of the negative inotropic effect of this drug. There exist important clinical impressions which seem to confirm the correctness of this appraisal (Pines[22]). The present

experiments seem to afford additional evidence that khellin has considerable negative influence upon the chrono- and dromotropic properties of the heart. It can lead as well to subendocardiac lesion and has a certain cumulative action. In regard to excitability, we were under the impression that this was increasing slightly after the administration of khellin but we do not possess any direct proofs.

1. The influence of the khellin upon the chronotropic property of the heart, i.e., upon the impulse formation, affects not only the sinoauricular node, but also the auriculoventricular node and all lower centers. This is obvious from the fact that we were able to observe frequently, after the administration of khellin, the total standstill of the ventricles. Similarly, if khellin was injected after some other drug, which inhibits auriculoventricular conduction, like digitalis, strophantin, or methylene blue, frequently after a short period of complete auriculoventricular block, we had to deal with the arrest of the ventricles and only the atria continued beating.

With reference to the mechanism of this influence paralyzing the discharge of the stimuli, we can affirm it is only partially dependent on the stimulation of the vagi. The other part has to consist in the direct activity upon the specific fibers. In this respect we can quote the results of our experiments with the section of vagus and with the administration of paratropine and methylene blue.

2. Under the influence of khellin there appeared in the present study the following disturbances of the conduction: incomplete auriculoventricular block, partial auriculoventricular block, Grade 1 and 2, interauricular and interventricular block. All these phenomena demonstrate that the inhibition affects the conduction in the specific system as well as in the ordinary cardiac fiber. In favor of this latter are the observations of the interauricular block recorded by us in the course of the present study and the curves, the pattern of which in our judgment, could derive from the existence of the sinoauricular block. In the case of the conductivity the vagal participation is perhaps slightly greater than it is in the case of impulse formation.

3. The capacity of khellin to create a subendocardiac lesion has manifested itself within the auricular and ventricular complexes by a monophasic deviation of the S-T segment, which occurred many times after khellin administration. This property, similarly with some others, khellin has in common with digitalis. In case of digitalis the mechanism of the appearance of subendocardiac lesion is unknown (Sodi-Pallares).[10] Some authors, as for instance Schaefer,[9] are inclined to think that the excitation wave is being extinguished prematurely in the fibers which are normally stimulated at the end of the accession stage. Also according to the last mentioned author there is no reason to consider that the QRS changes should necessarily coexist with the alterations of the S-T segments, because the power of the monophasic potential relies principally on its long duration and the time integral of S-T deviation is about 300 times longer than the time integral of the current of R waves of the affected fibers ("Da das monophasische Potential in seiner vollen Staerke fast 0.3 sec. lang besteht, die R Zacke nur 1 msec. lang ist, ist das Stromzeitintegral der ST Senkung rund 300 mal groesser als der Ausfall an QRS"). Nevertheless, in our case, i.e., after the khellin injection, we could

record within the auricular QRS the increase of the positivity, diminution of the negativity and the augmented delay of intrinsic deflection, or in other words, the triad of the lesion (Sodi-Pallares).[10]

4. The property of the cumulative action of khellin is very important, particularly from the practical point of view. The essence of the cumulative action is also unknown even in the case of digitalis. Historically, it was thought that the digitalis glucosides are stored in heart muscle so that the effect of the lastly administered dosage is derived simply from the addition of this dosage to the dosages preserved in storage (the chemical cumulative effect). However, due to investigations of Lewitzky,[23] Buechner,[24] Bauer and Fromherz[25] and of others, we know now that there is also a cumulative effect depending on summation not of quantities but of activities of different dosages. This would be due to the fact that a sufficiently large dose of digitalis would produce alterations of cardiac fibers and the heart's response to later administration would be stronger than to a dose administered previously (allobiotic response according to Hoesslin).[26] In regard to khellin, the cumulative effect has been observed by every author and quantitatively estimated by Anrep and associates.[7]

We have also been able to observe the augmented effect of the second or third administration of khellin upon the chrono- and dromotropic properties of heart muscle as well as in respect to its capacity to create a subendocardiac lesion. Anrep and associates[7] pointed out that 4 days after the administration of khellin one could still find small quantities of this drug about equally distributed between blood and organs without mentioning specifically the heart muscle. However, the deep alterations in heart muscle, which occur under the influence of khellin and can be recorded electrocardiographically, suggest that on top of the chemical cumulative effect there exists probably the addition of activities.

5. With reference to the bathmotropic property, one can say nothing decisive on the basis of the present study.* Sometimes we had the impression that after khellin it was a little more difficult to produce by means of ouabain injections the appearance of ventricular fibrillation. Another time, as for example, in the horse, we have observed the access of ventricular paroxysmal tachycardia under the influence of khellin. With digitalis, the impression gained by us, was different from that in the experiments with ouabain, because it seemed to us the ventricular extrasystoles after the khellin and digitalis were appearing earlier than when digitalis only was administered. However, it appears safe to point out that khellin does not inhibit the ventriculofibrillatory capacities of digitalis glucosides.

6. There exists a synergism between the khellin on the one hand and digitalis, ouabain, methylene blue, and dioxyline phosphate on the other in respect to the negative dromo- and chronotropic effects, and the capacity to induce the subendocardiac lesion.

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*In this respect it should be perhaps also recalled that digitalis definitely reduces the excitability of the heart (Scherf and Schott).[27]

SUMMARY AND CONCLUSIONS

An electrocardiographic study of the influence of khellin upon the heart of mammals has been carried out. During this study the following observations could be made:

1. Khellin has a negative influence upon the chrono- and dromotropic properties of the heart muscle; the action upon the bathmotropic property was not so clear, whereas the capacity of creating the subendocardiac lesion seems to be established.

2. The effects of khellin upon the chrono- and dromotropic qualities of the heart muscle add themselves under propitious circumstances to those of digitalis, ouabain, methylene blue, and mercurial diuretics. Also, khellin seems to make the heart more sensitive to the ventriculofibrillating action of the mercurial diuretics and of dioxyline phosphate.

Moreover, on the basis of the present study, as well as of the clinical experience and reasoning, one can probably make the following suggestions: it is not recommended to use khellin in the presence of disturbances of the sinoauricular, auriculoventricular, and intraventricular conduction, or in the postinfarction states, or in cardiac insufficiency.

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THE SIGNIFICANCE OF T-WAVE INVERSION IN SINUS BEATS FOLLOWING VENTRICULAR EXTRASYSTOLES

RICHARD H. MANN, M.D.,* AND HOWARD B. BURCHELL, M.D.**

ROCHESTER, MINN.

CHANGES in both voltage and direction of the T waves of the sinus beats immediately following ventricular extrasystoles (premature ventricular contractions) were first reported by White.[1] Isolated subsequent reports have called attention to these phenomena.[2-9] Changes in amplitude of the T waves of such sinus beats may be manifested by either an increased or a decreased positivity or negativity as compared to the configuration of T waves in the sinus beats either preceding or remote from the ventricular extrasystoles. Such minor variations are comparatively frequent. A less frequent phenomenon is a frank reversal in the direction of the T waves in the sinus beats immediately following ventricular extrasystoles.

Scherf[6] and Levine and associates[9] have reported a large group of cases in which such changes in the T waves occurred following premature contractions, the studies including cases of both auricular and ventricular extrasystoles. A high incidence of heart disease was present in the groups as a whole, regardless of the direction of the changes in the T waves of the postextrasystolic beat. Scherf noted an even greater incidence of heart disease, however, in those cases in which the T wave became (1) less positive, (2) more inverted, or (3) reversed to negativity in the sinus beats following the premature contractions. Of particular pertinence in our study was the fact that heart disease was reported to be present in all of the ten cases in which inversion of otherwise upright T waves was present in the sinus beats immediately following ventricular extrasystoles.

In a previous study of 450 patients showing frequent ventricular extrasystoles who had been seen in the electrocardiographic laboratory at the Mayo Clinic, alteration in the amplitude of the T waves of the postextrasystolic sinus beats was noted in a minority of cases.[10] The degree of change in the amplitude of the T waves varied greatly. When these patients were considered as a group, the presence of a change in amplitude alone of the T waves in the sinus beats following ventricular extrasystoles did not appear to have any diagnostic importance. In five of the 450 patients (1.1 per cent) the T waves were frankly inverted in the sinus beats immediately following ventricular extrasystoles,

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*Fellow in Medicine, The Mayo Foundation, part of the Graduate School of the University of Minnesota.

**Division of Medicine, Mayo Clinic, Rochester, Minn.

while the T waves preceding and remote from the extrasystoles were upright. In this further study, the diagnostic significance of such frank inversion of T waves following ventricular extrasystoles is considered.

MATERIALS AND METHODS

This report is concerned with electrocardiographic records from the clinic in which the T waves of the sinus beats following ventricular extrasystoles were frankly inverted and the T waves of the sinus beats elsewhere in the same lead were definitely positive. No cases were included in which auricular fibrillation was present. A group of forty-six cases was collected from current routine tracings during the years 1950 to 1952, inclusive.

The clinical records were reviewed, and the patients were classified as to the presence or absence of heart disease according to the criteria below.

Systolic blood pressures of 170 mm. Hg or more or a diastolic pressure of 90 mm. or more, or both, were the criteria for hypertension. Collateral evidence for the presence of significant hypertension was available from examinations of the ocular fundi, chest x-rays, or electrocardiograms in the majority of these patients.

A second group of patients, classed as having coronary arterial disease, included those who had angina pectoris or previous myocardial infarction or patients who had atypical chest pain but definite electrocardiographic abnormalities.

A third group included patients who presented evidence of valvular heart disease. A fourth group consisted of two patients who had heart disease, to be described later, that did not fit into the preceding categories. The remaining patients were classed as having no evidence of heart disease.

All the electrocardiograms studied included at least the standard limb leads and three precordial leads; in approximately one-half these patients, more extensive electrocardiographic study had been done. The electrocardiograms were divided into three groups, namely, normal tracings, those with minor abnormalities, and grossly abnormal tracings. Minor abnormalities in this series included such changes as prolonged P-R intervals and isoelectric or diphasic T waves in a single lead in which the T waves are normally upright.

For comparison of the incidence of heart disease, the records in a group of forty-six patients showing frequent ventricular extrasystoles but *without* subsequent changes in the T waves were selected to match this group as to age and sex distribution.

RESULTS

The average age of the forty-six patients showing inversion of T waves in the sinus beats following ventricular extrasystoles was 59 years; the oldest was 76 and the youngest 34. Twenty-nine were men and seventeen were women.

Of the forty-six patients in this series, forty-three (93 per cent) had evidence of heart disease. Three patients (7 per cent) had no evidence of heart disease according to the criteria used in this study. One of them, a man, aged 65, had a blood pressure that varied from 135 to 155 mm. Hg systolic and from 85 to 90

diastolic. In the absence of any supportive evidence, this patient was not classed as hypertensive. The second patient, a man aged 69, had nearly isoelectric T waves in standard Lead I. The third of these patients, a woman aged 61, had no clinical evidence on which the diagnosis of heart disease could be based.

TABLE I. INCIDENCE OF HEART DISEASE IN 46 PATIENTS WHO HAD INVERSION OF T WAVES IN THE SINUS BEATS FOLLOWING VENTRICULAR EXTRASYSTOLES

TYPE OF HEART DISEASE	PATIENTS
Hypertensive	24
Coronary arterial	14
Valvular	3
Miscellaneous	2
No disease	3

The various types of heart disease encountered in the entire group are summarized in Table I. In the miscellaneous group was a patient who had dystrophia myotonica and an abnormal electrocardiogram (Fig. 1). The other patient in this category had the history of hyperthyroidism and congestive cardiac failure. When examined here, approximately a year after a thyroidectomy elsewhere, this patient complained of only moderate exertional dyspnea and had minor electrocardiographic abnormalities (isoelectric T waves in standard Lead II).

The same criteria were used in classification as to the presence or absence of heart disease in the control group of forty-six patients chosen because their records had frequent ventricular extrasystoles but did not have postextrasystolic changes in the T waves. The incidence of heart disease in this control group was 57 per cent. Of the twenty-six patients classed as having heart disease, fifteen (58 per cent) were classed as hypertensive, ten (38 per cent) as having coronary arterial disease, and one (4 per cent) as having valvular disease.

In the group of forty-six patients who did show transient inversion of the T waves, seventeen (37 per cent) had otherwise normal electrocardiograms. Minor electrocardiographic abnormalities were present in twelve patients (26 per cent), and grossly abnormal electrocardiograms were present in seventeen (37 per cent).

Inversion of the T waves in the sinus beats following ventricular extrasystoles was usually not observed in all the leads of an electrocardiogram in which premature contractions occurred. When inversion occurred in a given lead, however, it was present consistently in the sinus beats following all the ventricular extrasystoles in that lead. In two cases, when such inversion was present in a given lead, it was present on subsequent electrocardiograms taken some months later. The reverse was true in one patient who had been diagnosed as having coronary insufficiency and in whom inversion of the T waves was present following ventricular extrasystoles in Lead V_3 on his initial visit. On subsequent examination a year later, the control electrocardiogram taken before the performance of an exercise test showed no change in the T wave of the sinus beat

following a ventricular extrasystole in Lead V_3. The electrocardiogram taken immediately after exercise showed changes characteristic of myocardial ischemia, but no ventricular extrasystoles were present. An electrocardiogram taken after five minutes' rest again showed inversion of the T wave in the sinus beat following a ventricular extrasystole in Lead V_3.

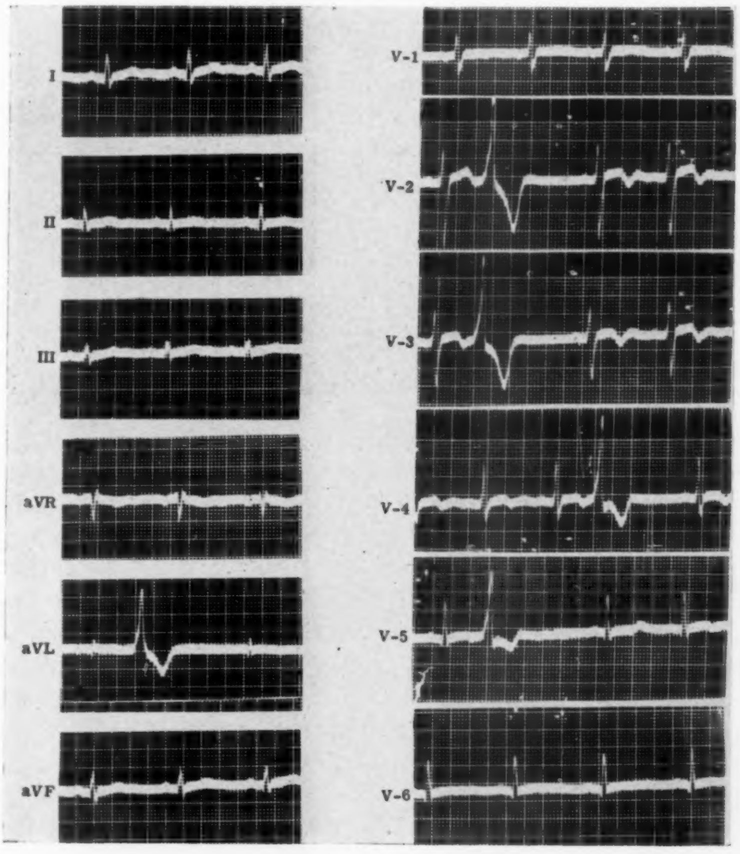


Fig. 1.—Electrocardiographic changes in a 42-year-old man who had dystrophia myotonica. Note the persistent inversion of the T waves following the ventricular extrasystole for two sinus beats in Lead V_2. The T waves were diphasic or inverted preceding the ventricular extrasystoles in Leads V_3, V_4 and V_5. The T wave became more inverted following the ventricular extrasystoles in Leads V_3 and V_4, but it became more upright in Lead V_5.

Inversion of T waves following ventricular extrasystole was observed in only one lead of a given electrocardiogram in thirty patients (65 per cent), in two leads in ten (22 per cent) and in three leads in six (13 per cent). The maximal inversion of the T wave of the sinus beat following the ventricular extrasystole did not exceed 4 mm. (0.4 mv.). The leads in which inversion of T waves were observed are summarized in Table II. The depth of the T-wave inversion did not appear to correlate with the presence or absence of heart disease, the depth of the inversion being just as great in the three patients without clinical heart disease.

No correlation was established between a specific lead or the number of leads in which inversion of the T waves occurred and the presence or absence of heart disease. In the three patients who were classed as having no clinical evidence of heart disease, inversion of the T wave in the sinus beat following a ventricular extrasystole occurred in Lead III in one patient, in Lead V_5 in the second patient and in Leads III, V_1 and V_3 in the third.

TABLE II. LEAD RECORDS AVAILABLE FOR STUDY SHOWING VENTRICULAR EXTRASYSTOLES AND INVERSION OF T WAVES IN THE SUCCEEDING SINUS BEAT

LEAD	INCIDENCE OF INVERSION
I	6
II	5
III	11
aV_L or aV_F	3
V_1 or V_2	4
V_3 or V_4	15
V_5 or V_6	24
Total	68 (46 patients)

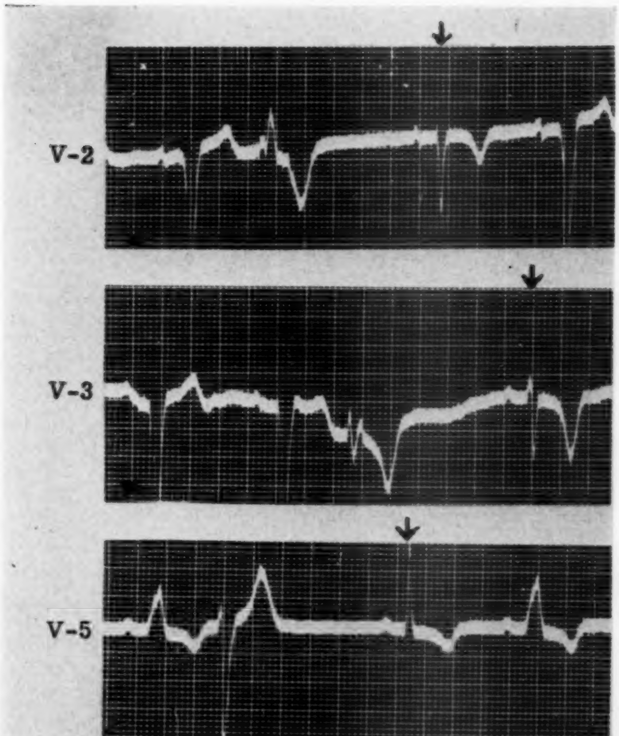
In all but two of the forty-six patients, inversion of the T wave was observed only in the sinus beat immediately following the ventricular extrasystole, with reversion to an upright deflection in the succeeding sinus beats. In one patient, the inversion persisted for two beats following the ventricular extrasystole and in the other it persisted for three beats. In other patients, the amplitude of the positive T wave in the second and, rarely, the third sinus beat following the inversion occasionally was decreased as compared to the amplitude of the T waves of the sinus beats elsewhere in the same lead.

In two patients, inversion of the T wave occurred following a ventricular extrasystole only in the presence of interpolation. In one of these patients who had noninterpolated ventricular extrasystoles in the same lead, no change was present in the sinus beat following such noninterpolated contractions.

Of the seventeen patients classed as having grossly abnormal electrocardiograms, four had bundle branch block; left bundle branch block was present in three, and right bundle branch block in one. These tracings had in common the finding that the sinus beats immediately following the ventricular extrasystoles showed a normal intraventricular conduction time with inversion of the T wave (Fig. 2).

Several associated features were observed in this group of electrocardiograms in addition to the inversion of T waves. One tracing showed prolongation of the Q-T interval in the sinus beat following a ventricular extrasystole (Fig. 3). In one patient inversion of the T wave following a ventricular extrasystole appeared "to anticipate" by some weeks the appearance of constant inversion of the T waves (Fig. 4). One patient showed elevation of the S-T segment as well as inversion of the T waves in the sinus beats following ventricular extrasystoles (Fig. 5).

Fig. 2.



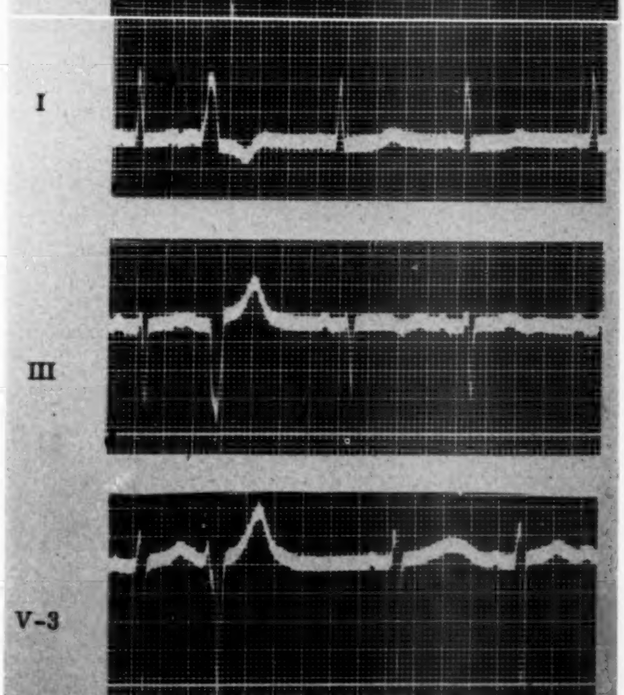


Fig. 3.

Fig. 2.—Disappearance of left bundle branch block and inversion of the T waves in the sinus beats following ventricular extrasystoles in a 54-year-old patient who had hypertension and roentgenographic evidence of cardiac enlargement.

Fig. 3.—Prolongation of the Q-T interval in the sinus beats following ventricular extrasystoles in a 70-year-old patient who had known hypertension of long duration. This is most clearly seen in Lead V_3. Prominent U waves are present in the last sinus beats in Leads III and V_3. The T wave is inverted in the sinus beat following the ventricular extrasystole in Lead III.

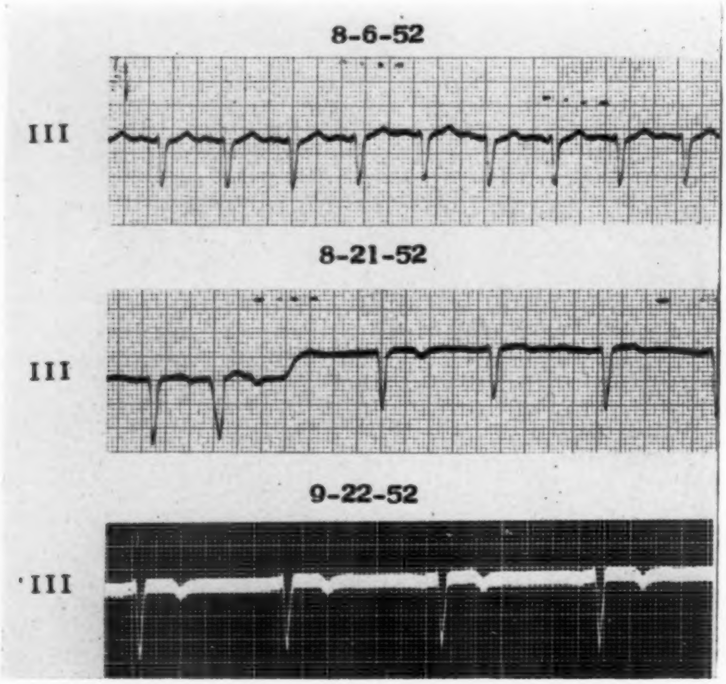


Fig. 4.—Lead III in serial tracings from a 52-year-old man who had known hypertension and recent attacks of prolonged precordial pain. Note that inversion of the T wave first occurred in a sinus beat following a ventricular extrasystole (8-21-52). Later the T waves became consistently inverted in all the sinus beats (9-22-52).

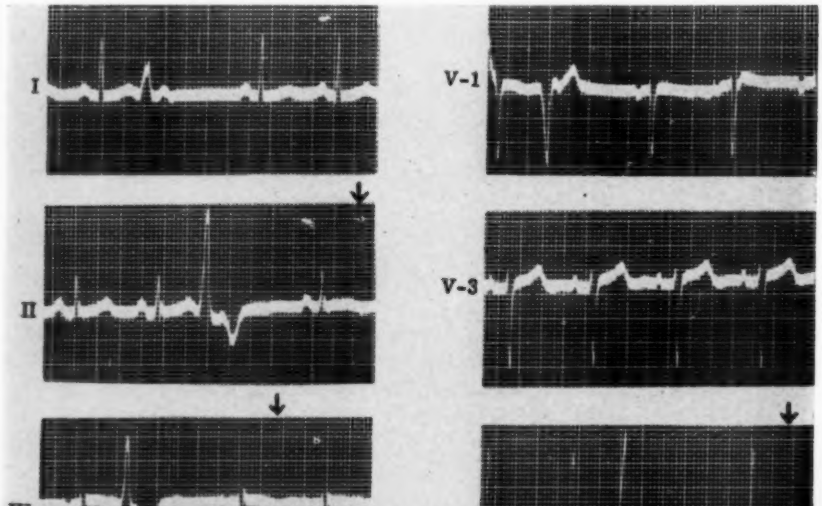


Fig. 5.—Elevation of the RS-T segments as well as inversion of the T waves in the sinus beats following ventricular extrasystoles in a 54-year-old woman who had hypertension and evidence of cardiac enlargement on x-ray. After the ventricular extrasystoles in Leads II and III, slight elevation of the RS-T segment and inversion of the T waves are noted. In Lead V_5, frank inversion of the T wave occurs in the sinus beat following the extrasystole. Other than the changes mentioned, this would be classed as a normal tracing.

COMMENT

The evidence presented suggests that inversion of the T wave in sinus beats following ventricular extrasystoles should be regarded as presumptive evidence of heart disease. To our knowledge, only one patient has been reported on in the literature in whom this change has occurred in the probable absence of heart disease.[7] The three patients classed as normal in this series doubtfully might be added. Despite the ages of these three patients and the presence of borderline abnormalities in two, there were no definite findings of clinical heart disease. Since inversion of the T waves following ventricular extrasystoles was observed frequently in otherwise normal tracings or tracings showing only minor abnormalities, the finding may be helpful in alerting the observer as to the probable existence of heart disease. If supportive clinical evidence is absent, further investigation, such as an exercise test, might be indicated. Levine and co-workers noted a correlation between postextrasystolic T-wave changes of any type and positive results of the Master's "two-step" test. It is apparent from the diverse types of heart disease associated with the described inversions of T waves that this change is etiologically nonspecific.

The mechanisms involved in the inversion of T waves following ventricular extrasystoles are obscure. The various possibilities have been reviewed by Scherf[6] and by Levine and his group.[9] It was Scherf's opinion that the most likely explanation is related to the prolonged pause following the extrasystole, resulting in prolonged filling and increased diastolic size, an altered ventricular gradient might occur and result in inversion of the T wave.

A prolonged period of diastolic filling cannot be the only explanation. In interpolated ventricular extrasystoles followed by inversion of the T wave (without changes in the QRS complexes) in the succeeding sinus beat, the period of diastolic filling is shortened. If it were presumed that the ventricular extrasystoles were completely ineffective beats as far as cardiac output is concerned, the total period of diastolic filling still is less than in a normal sinus cycle, unless there were an unusual degree of lengthening of the P-R interval of the postextrasystolic beat. It would appear as if the preceding abnormal excitation pathways of the ventricular extrasystole in some way caused a reversal of the repolarization pattern. Reduction of coronary flow related to a single ventricular extrasystole would appear to be an unlikely explanation because of the transient nature of the changes.

The prolongation of the Q-T interval in the sinus beats following ventricular extrasystoles in one patient suggested a disturbance in the uniformity in rate of repolarization (Fig. 3). Levine and associates have noted similar cases and attribute the prolongation to the incorporation of U waves into the latter part of the T waves. The elevation of the RS-T segments following ventricular extrasystoles in one patient suggested the type of change seen in myocardial injury (Fig. 5). No single mechanism apparently suffices to account for all the observed changes. In the over-all appraisal of the significance of the phenomenon of transient inversion of T waves, it is to be noted that such inversion is really of

infrequent occurrence in the presence of heart disease. Thus, it would appear that an unusual set of circumstances must be present to produce inversion of the T waves as well as the other observed changes.

Prolonged disappearance of bundle branch block following a ventricular extrasystole has been reported.[11] Scherf and Schott[12] have observed the disappearance of intraventricular conduction defects (bundle branch block) in the post-extrasystolic sinus beat. The four patients encountered in this study who had bundle branch block showed a similar absence of bundle branch block limited to the sinus beats after the extrasystoles. The phenomenon was constant in all the tracings, occurring after each ventricular extrasystole. In one patient in whom serial electrocardiograms were available, the ventricular extrasystoles apparently were of multifocal origin, and the sinus beats after the extrasystoles consistently showed normal conduction, giving evidence that this change is related to the pause after the extrasystole and not to the specific nature of the extrasystole itself. It has been demonstrated in certain cases of bundle branch block that slowing of the sinus rhythm, as induced by pressure on the carotid sinus, may abolish the defect in conduction.[13] It is apparent that our four patients who had bundle branch block did not have the same type of inversion of the T waves following ventricular extrasystoles that was present in the remainder of the series.

It appears important that the diagnosis of myocardial disease can be made on the basis of the configuration of a complex of a beat after an extrasystole (Fig. 2).

Electrocardiographic changes have been reported in dystrophia myotonica.[14,15] The changes have been attributed to possible cardiac involvement in the dystrophic process or to coronary arterial disease. In our opinion, it appears more likely that these changes are in some way related to myocardial involvement rather than to coincident coronary arterial disease. A similar process has been postulated for the cardiac involvement found in Friedreich's ataxia.[16] This patient in our series was a 42-year-old man who came to the clinic because of muscular wasting. He presented the characteristic clinical picture of dystrophia myotonica and had no symptoms referable to the cardiovascular system. The blood pressure was 120 mm. Hg systolic and 80 diastolic. He was classed as having heart disease on the basis of an abnormal electrocardiogram (Fig. 1).

SUMMARY

Heart disease was present in 93 per cent of a series of forty-six patients encountered at the Mayo Clinic who had inversion of the T waves in the sinus beats following ventricular extrasystoles. In 63 per cent of these patients, the electrocardiograms were otherwise normal or showed only minor associated abnormalities.

The incidence of heart disease in a control group of patients, matched in regard to age and sex with the above group, who had frequent ventricular extrasystoles without changes in the T waves, was 57 per cent.

Four patients who had bundle branch block showed normal intraventricular conduction with inversion of the T waves in the sinus beats immediately following ventricular extrasystoles.

One patient who had dystrophia myotonica showed electrocardiographic abnormalities as well as inversion of the T waves following ventricular extrasystoles.

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THE DURATION OF THE T WAVE AND ITS RELATION TO THE CARDIAC RATE IN HEALTHY ADULTS

DESIDERIO GROSS, M.D.

SANTIAGO, CHILE

ALTHOUGH the height of the T wave has been thoroughly studied and exactly established in different leads, its duration has been dealt with by the investigators so far only occasionally. Most of the textbooks consulted do not even mention the normal duration of the T wave. According to Scherf and Boyd[1] the duration of the T wave varies greatly. Graybiel and White[2] state that its duration in the second lead is 0.10 to 0.25 sec. The figures given by other authorities are: Wiggers,[3] 0.20 sec.; Luisada,[4] 0.16 to 0.25 sec.; Dressler,[5] 0.15 to 0.20 sec.; Cossio,[6] 0.12 to 0.24 sec. However, all the authorities agree that the exact determination of the duration of the T wave is often very difficult, or almost impossible to make, because of graphic reasons. In fact, any accurate determination of the origin of the T wave is practically impossible when there is a slow transition of the S-T segment into the ascending limb of the T wave, or when the ascending limb of the S and T waves forms a straight line. Besides these technical difficulties, which are real, there is still another point which has not attracted attention so far. The duration of the T wave has been expressed in a manner similar to that of its height, i.e., without relation to the cardiac rate. Therefore, the variation of the values has been discouragingly wide and seemingly unpredictable.

The present study has been based on these well defined criteria. Duration of the T wave was measured in those cases only which allowed accurate measurement. The possible correlation between duration of this wave and the cardiac rate also was studied. As a result, a quantitative correlation could be established between the duration of the T wave and the cardiac cycle, and the Q-T interval.

METHOD

As a matter of fact the determination of the duration of the T wave is neither difficult nor especially inaccurate in those cases in which it is technically practicable. In other cases it is impracticable and such records must be simply eliminated and not used for measurement. Measurable records are those where the ascending limb of the T wave forms a definite angle with the RS-T

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segment and where because of the presence of a clearly visible kink delimitation is possible within 0.01 to 0.02 sec. Immeasurable records are those in which there is a gradual transition of the RS segment into the T wave, in which the T wave is of low voltage and in which RS-T is a straight line. As already stated, the present study is based exclusively on measurable records, eliminating those with inaccurate measurements. The proportion of measurable and immeasurable records was 2:1.

For the present study, normal records of healthy individuals, male and female, were selected who presented no clinical or laboratory evidence of any cardiac abnormality. Length of the cardiac cycle and of the Q-T interval and height and duration of the T wave were measured in the second lead only where the T wave is usually tallest and so measurement could be made more easily. Records were divided into groups of 30 according to cardiac rates of 51 to 120. In each group average values were calculated.

RESULTS

Table I reproduces the average values. Duration of the T wave shows a definite correlation with the cardiac rate. The largest average duration of 0.177 sec. was found in the group with the longest cardiac cycle, i.e., at the lowest cardiac rate of 51 to 60 beats per minute. T wave of shortest duration with an average of 0.134 sec. was found in the group with shortest cardiac cycle, i.e., at greatest cardiac rate. Between both extremes the average duration of the T wave shows a direct correlation with the duration of the cardiac cycle and an inverse correlation with the cardiac rate. The range of the measured duration of the T wave in the 210 cases studied was 0.11 to 0.23 sec.

Table II shows the correlation found between height and duration of the T wave. On account of the relatively small number of cases in each group of cardiac frequencies (30) it seems wise to refer only to a "tendency" but not to an exactly established quantitative correlation. T waves of largest duration were found in cases of high T waves, and shortest when T waves were small. This behavior can clearly be seen in the group of cardiac frequency from 61 to 70; average duration of the T wave was of 0.16 sec. with a height of 1 to 2 mm. The average duration of the T wave increased to 0.163 sec. when the height of the T wave increased as it occurred in the group of T waves with a height of 2 to 3 mm. In the group of T waves with a height of 3 to 4 mm. the average duration of the T wave was 0.175 sec., and in the group of T waves with a height of 3 to 4 mm. it was 0.180 sec. The same correlation between height and duration of the T wave was seen in every group of cardiac frequency studied.

In further studies two other quantitative correlations have been established: a correlation between the duration of the T wave and the Q-T interval, and a correlation between the duration of the T wave and the cardiac cycle.

Correlation Between the Duration of the T Wave and the Q-T Interval.—When the duration of the T wave was compared with the length of the Q-T interval of the same ventricular complex the average duration of the T wave

TABLE I. THE DURATION OF THE T WAVE AND ITS RELATION TO THE CARDIAC CYCLE AND TO THE Q-T INTERVAL (AVERAGE VALUES)

CARDIAC RATE (MIN.)	AGE (YR.)	R-R (SEC.)	T WAVE HEIGHT (MM.)	T WAVE DURAT. (SEC.)	Q-T (SEC.)	$\frac{Q\text{-}T}{2}$ (SEC.)	DIFF. $T - \frac{Q\text{-}T}{2}$ (SEC.)	S.D.	RANGE	T DUR. CALCULATED (SEC.)	DIFF. T DUR. MEAS./CALC. (SEC.)	S.D.	RANGE
51–60	41.3	1.053	3.45	0.177	0.372	0.186	+0.0089	±0.0148	−0.02 +0.05	0.185	+0.008	±0.0167	−0.04 +0.04
61–70	41.5	0.908	2.90	0.164	0.353	0.176	+0.0120	±0.0093	0.00 +0.03	0.170	+0.006	±0.0162	−0.04 +0.03
71–80	41.2	0.791	3.17	0.161	0.344	0.172	+0.0113	±0.0062	0.00 +0.02	0.159	+0.001	±0.0104	−0.02 +0.02
81–90	38.8	0.700	2.47	0.149	0.320	0.160	+0.0106	±0.0097	−0.02 +0.03	0.150	0.000	±0.0135	−0.04 +0.02
91–100	39.6	0.635	2.45	0.147	0.312	0.156	+0.0090	±0.0036	0.00 +0.01	0.143	−0.003	±0.0087	−0.02 +0.01
101–110	41.5	0.568	2.45	0.145	0.304	0.152	+0.0070	±0.0094	−0.01 +0.02	0.136	−0.008	±0.0142	−0.03 +0.02
111–120	39.5	0.523	2.55	0.134	0.286	0.143	+0.0085	±0.0096	−0.01 +0.03	0.132	−0.002	±0.0099	−0.02 +0.01

Table II. The Correlation Between Height and Duration of the T Wave

	Cardiac Rate (min.)	Height of the T Wave (mm.)								
		0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
Duration (sec.) No. of cases	51–60	0.170 1	0.171 8	0.166 8	0.183 6	0.193 3	0.200 1	0.185 2		0.200 1
	61–70		0.160 7	0.163 18	0.175 2	0.180 1	0.180 2			
	71–80		0.160 6	0.158 12	0.163 7	0.162 4	0.180 1			
	81–90	0.142 4	0.147 13	0.153 6	0.158 5	0.150 1		0.150 1		
	91–100	0.145 2	0.146 12	0.145 11	0.150 5					
	101–110	0.130 5	0.142 12	0.147 8	0.160 4				0.170 1	
	111–120	0.128 4	0.134 10	0.137 10	0.136 5				0.140 1	

was found to be approximately 0.01 sec. less than one-half the duration of the corresponding Q-T interval:

$$\text{T dur.} = \frac{\text{Q-T}}{2} - 0.01.$$

This correlation was found to be valid throughout all the studied cardiac rates. Table I reproduces the average lengths of the T waves and one-half the durations of the Q-T intervals, and their mean differences with the corresponding standard deviations. According to these data one-half the duration of the Q-T interval was at every cardiac rate larger than the duration of the T wave. The average difference was +0.0096 sec. with a range of +0.007 to +0.012.

Correlation Between the Duration of the T Wave and the Cardiac Cycle.— The results obtained in the present study make it clear that the main factor determining the duration of the T wave is the length of the cardiac cycle. A mathematical analysis revealed that the correlation between the duration of the T wave and the length of the corresponding cardiac cycle can be expressed satisfactorily by the equation:

$$\text{T dur.} = 0.08 + \frac{\text{RR}}{10}.$$

This equation means that to obtain the duration of the T wave in hundredths of a second, one tenth of the cardiac cycle has to be added to the constant 0.08. For example, if RR is 0.80 sec., the T dur. = 0.08 + 0.80/10 = 0.08 + 0.08 = 0.16 sec. The average duration of 30 measured T waves was 0.159 sec. (see Table I). Calculated durations of the T wave were somewhat larger at low cardiac rates of 51 to 90, and somewhat shorter at high cardiac rates of 91 to 120. Average differences and their standard deviations are reproduced in Table I.

DISCUSSION

Two circumstances explain why the duration of the T wave so far has not been well studied in the electrocardiographic practice: First, because measurements were tried in all records including those where there was no possibility of an exact determination; secondly, because the duration of the T wave was expressed regardless of the cardiac rate and therefore numerical values varied within wide limits. The graphic pecularities of the RS-T segment limit the possibility of an accurate measurement of the duration of the T wave. It is therefore necessary to bear in mind the fact that there are measurable and immeasurable records. Different methods were proposed to ascertain the origin of the T wave in cases of a gradual transition of the ascending limb but this technical problem still remains unsolved. Lepeschkin and Surawicz[7] have suggested that the point indicating the origin of the T wave is at the maximal distance from a line connecting the peak of the T wave with the RS-T junction. Other arbitrary criteria also have been proposed for the same purpose, but their value is open to discussion.

On the other hand, the duration of the T wave must be related to the cardiac rate, in opposition to its height that shows no definite correlation with the heart

rate. The Q-T interval in itself has no definite significance being only related to the cardiac rate similar to the behavior of the duration of the T wave. The main factor that determines the duration of the T wave is the length of the cardiac cycle. This could be established in the present study in a very convincing manner. The height of the T wave exerts a modifying influence on the duration, lengthening it in cases of greater height and shortening it with decreasing height. But these secondary modifications do not interfere with the fundamental correlation which exists between the duration of the T wave and the cardiac cycle.

SUMMARY

1. For graphic reasons the duration of the T wave can not be measured in every record. Thus, records must be divided into two groups: measurable and immeasurable ones. The present study was based exclusively on measurable records.

2. The duration of the T wave is determined mainly by the length of the cardiac cycle; this correlation is a quantitative one. The height of the T wave influences its duration in a definite sense but not in a predictable form.

3. The duration of the T wave can only be evaluated in relation to the cardiac cycle, in a similar manner as that of the Q-T interval.

4. The duration of the T wave presents the following two quantitative correlations: (a) On an average it is one-hundredth of a second less than the one-half duration of the corresponding Q-T interval; T dur. = Q-T/2 − 0.01; (b) on the other hand, its relation to the cardiac cycle is expressed by the equation: T dur. = 0.08 + RR/10.

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TRANSIENT ELECTROCARDIOGRAPHIC CHANGES IDENTICAL WITH THOSE OF ACUTE MYOCARDIAL INFARCTION ACCOMPANYING ATTACKS OF ANGINA PECTORIS

Hugo Roesler, M.D., and William Dressler, M.D.

Philadelphia, Pa., and Brooklyn, N. Y.

LIGATION of a coronary artery in the dog causes infarction in the area of the myocardium which is cut off from its blood supply. This is manifested in the electrocardiogram by deviations of the S-T segment, alteration of the T wave, and characteristic changes of the QRS complex.[1,2] When occlusion of a coronary artery in the dog is maintained for no longer than 20 minutes, it does not usually result in the production of a morphologic lesion in the myocardium, although the electrocardiogram may show changes "typical of myocardial ischemia" which may last for many days.[3] Bayley and associates[4,5] produced in the dog shortlasting total and subtotal occlusion of a coronary artery which resulted in the development of reversible electrocardiographic changes without microscopic lesions in the myocardium. After total occlusion, the first electrocardiographic changes appeared within 30 seconds. They consisted of sharp inversion of the T wave, which was termed "ischemia pattern." Within the next 60 seconds the S-T junction became elevated and the T wave upright, high, and peaked. These changes were referred to as "injury pattern." When subtotal occlusion was performed, the ischemia pattern could be converted into the injury pattern by increasing the degree of occlusion; conversely, on releasing the occlusion, the injury pattern changed to the ischemia pattern and then returned to normal. The ischemia pattern may be prolonged in proportion to the duration of the subtotal occlusion. Bayley and associates pointed out that the ischemia-injury patterns, although often observed with myocardial infarction in man, could not be regarded as diagnostic of infarction.[5] The ischemia pattern has been observed to exist in man as long as two weeks without detectable microscopic changes in the myocardium.[6]

Wilson and associates,[2] who studied the electrocardiographic changes which followed total and maintained occlusion of a coronary artery in the dog, concluded that "the characteristic QRS changes of coronary occlusion are due to death of the infarcted muscle." On the other hand, during brief coronary occlusion significant changes of QRS were never observed in association with the

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From the Departments of Medicine and Radiology, Temple University Medical School and Hospital, Philadelphia, Pa.; the Medical Services of the Maimonides Hospital in Brooklyn, N. Y., and the Department of Medicine, State University Medical Center at New York, N. Y.

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ischemia-injury patterns.[4,5] We want to report on two patients who, during attacks of angina pectoris, developed changes of QRS of the kind usually associated with myocardial infarction. The changes were transient. In one case they lasted only for a few minutes and subsided together with the anginal pain.

CASE REPORTS

CASE 1. F. H., a 55-year-old woman, had a family history of hypertension and coronary arteriosclerosis. Her parents and a brother died of coronary thrombosis. A sister suffered a myocardial infarction. Three other sisters had high blood pressure, two of them suffered cerebral accidents. Our patient was treated in 1948, at the age of 52, for urethral stricture and cystitis. She had no complaints from the heart at that time, and the cardiac findings including the electrocardiogram (Fig. 1, *A*)* were normal.

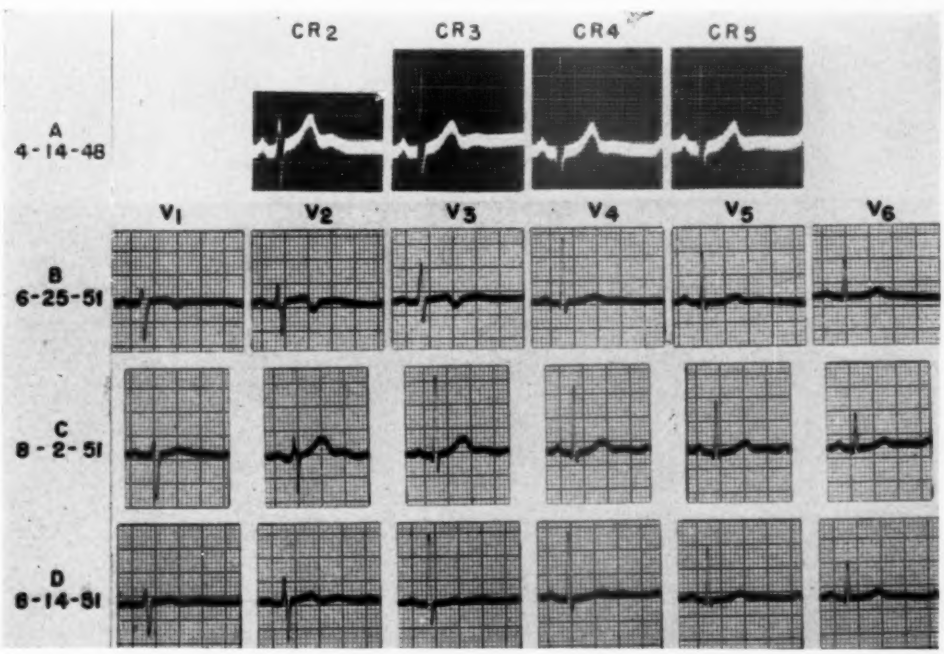

Fig. 1 (Case 1).—*A*, Normal tracing. *B*, Inverted T waves in Leads V_1 through V_3. *C*, T waves upright in all precordial leads, notched in V_1, blunted in V_2 through V_4. *D*, T waves diphasic and low in V_1 through V_3, notched in V_4.

In May, 1951, the patient began to experience chest distress in association with effort. Two weeks later similar attacks occurred when the patient dressed in the morning. Even when she rested she often felt a squeezing substernal pain which was associated with marked perspiration. The pain was relieved by nitroglycerine.

Physical examination on June 25, 1951, revealed no abnormal findings. The blood pressure was 100/70 mm. Hg. The blood cholesterol was 340 mg. in 100 c.c. The sedimentation rate (Wintrobe) was 10 mm./1 hour. The electrocardiogram (Fig. 1, *B*) showed inverted T waves in Leads V_1 through V_3, but no significant changes of QRS. Similar electrocardiographic findings had been observed by another examiner on May 21, 1951. The patient was advised to rest at

*Since the limb leads add no significant information, only the precordial leads are shown in the illustrations in order to save space.

home. An electrocardiogram taken by the family physician on July 19, 1951, was reported as showing signs of "improvement," inasmuch as the previously inverted T waves in the precordial leads had turned upright.

The patient was examined again on Aug. 2, 1951, after she had suffered, in the preceding five weeks, six or eight attacks of a heavy pressing sensation in the midchest associated with marked perspiration. One attack on July 29, which followed emotional strain, resulted in fainting, and the pulse was not perceptible for a short time. The electrocardiogram, taken on Aug. 2, 1951 (Fig. 1, *C*), showed upright, blunted T waves in Leads V_2 through V_4. The blood count was normal. The patient was permitted to increase slightly her physical activities. Subsequently her condition became worse. Anginal attacks occurred almost daily, and sometimes during the night. Nitroglycerine did not always help, and Demerol was occasionally required for relief. The patient was hospitalized on Aug. 14, 1951.

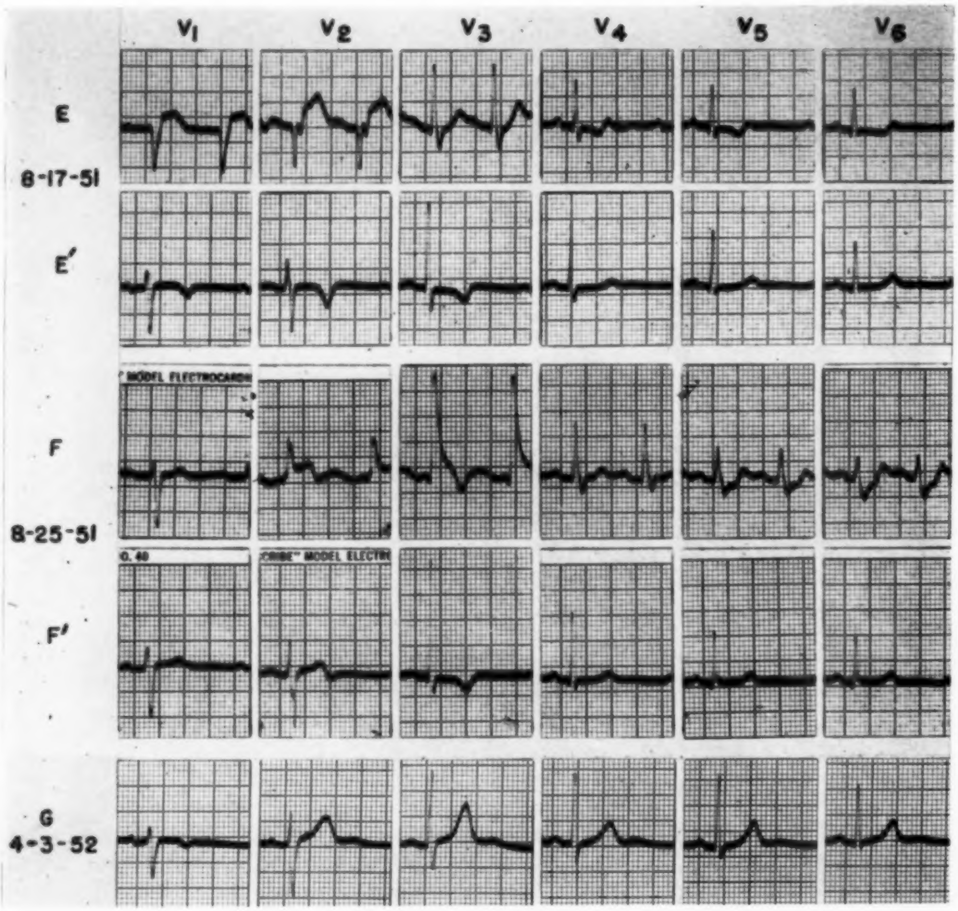

Fig. 2 (Case 1).—*E*, (During attack of anginal pain.) In Leads V_1 and V_2 the R deflection has disappeared, and S-T has shifted upward. T waves upright and rather high in V_2 and V_3. Reciprocal changes of S-T-T in V_4 through V_6. *E'*, (Immediately after tracing *E*, when the anginal pain had ceased.) In Leads V_1 and V_2 the R deflection has returned, and S-T has moved back toward the base line. Inversion of T in V_1 through V_3. *F*, (During attack of anginal pain.) In Leads V_2 and V_3 the S-T segment has shifted upward. Reciprocal depression of S-T in V_5 and V_6. No significant changes of QRS. *F'*, (A few minutes after *F*, when the anginal attack had ceased.) The S-T segment has moved back toward the base line. *G*, Normal tracing.

Physical examination revealed no abnormal findings. The blood pressure was 105/65 mm. Hg. An electrocardiogram on Aug. 14, 1951 (Fig. 1, *D*) showed lowering of T in the precordial leads. Besides, the T wave was diphasic in Leads V_1 through V_3, flat and notched in V_4.

During the period of hospitalization anginal attacks recurred, often requiring the administration of Demerol. The temperature and the sedimentation rate were normal. On Aug. 17, 1951, an anginal attack developed while an electrocardiogram was being taken. Nitroglycerine was given and the pain was relieved when the last precordial leads were recorded. During the anginal attack the tracing showed striking changes (Fig. 2, *E*). In the Leads V_1 and V_2 the R deflection disappeared, the S-T junction was elevated, and the T wave was upright and rather high in Lead V_2. Reciprocal changes of S-T-T were present in the Leads V_4 through V_6. After the electrocardiogram was completed and the anginal pain had ceased, another tracing was taken (Fig. 2, *E'*). It showed reappearance of the R waves and return of the S-T junction to the base line in the Leads V_1 and V_2. The T wave was inverted in the Leads V_1 through V_3. The sedimentation rate, on Aug. 17, 1951, was 10 mm./1 hour, and the temperature was normal.

Subsequently anginal attacks occurred at day and night time, most of them responding to nitroglycerine. In the night of Aug. 24, 1951, the patient suffered eight anginal attacks. The temperature remained normal, and the blood pressure unchanged. On Aug. 25, 1951, severe anginal pain developed while an electrocardiogram was taken; nitroglycerine was given immediately. The tracing (Fig. 2, *F*) showed in Leads V_2 and V_3 marked elevation of the S-T junction, followed by inverted T waves. The amplitude of R was not decreased. Reciprocal depression of S-T was noted in V_5 and V_6. An electrocardiogram, which was taken 10 minutes after the anginal pain had subsided, showed (Fig. 2, *F'*) return of the S-T segments to the previous level. The T wave was semi-inverted in Lead V_2 and inverted in V_3.

The sedimentation rate, on Aug. 30, 1951, was 32 mm./1 hour, and on Sept. 20, 1951, 30 mm./1 hour. During the month of September, the frequency of the anginal attacks gradually diminished, and the patient was discharged from the hospital at the end of September, 1951. Improvement continued while the patient was at home. There was one attack of angina in March, 1952; the electrocardiogram was normal. Part-time professional activities were resumed and were well tolerated. When the patient was examined on April 3, 1952, the blood pressure was 140/80 mm. Hg. The tracing (Fig. 2, *G*) showed normal findings. Subsequently the patient led a normal, active life. There were no complaints except for one anginal attack in May, 1953, in conjunction with emotional tension.

CASE 2. I. L., a 68-year-old man, was admitted to the hospital on Dec. 15, 1951. A week prior to admission, while walking, he experienced for the first time a squeezing pain across the upper part of the chest, which subsided when he rested. The pain returned when he started to walk again, and it took the patient an hour to make the way to his home, which he usually walked in 10 minutes. While he rested at home he was free of pain for two days. Then, attacks of anginal pain associated with perspiration occurred even during rest and lasted up to 30 minutes. The pain was promptly relieved by nitroglycerine. After admission to the hospital, attacks of chest distress recurred, lasting from 5 to 30 minutes. Some of the attacks were associated with nausea and marked perspiration.

The diagnosis on admission was: Acute onset of angina pectoris and impending myocardial infarction.

Anticoagulant therapy was administered. During the first two weeks the temperature remained normal. On Dec. 30, 1951, low grade fever developed which lasted for 6 days. The white blood cell count was normal. The sedimentation rate (Wintrobe) was increased throughout the six weeks period of hospitalization, ranging from 26 to 40 mm./1 hour.

Electrocardiograms taken on Dec. 18, 21, and 28, showed identical features. Only the tracing of Dec. 28, 1951, is shown (Fig. 3, *A*). It presented inversion of T in all precordial leads. On Jan. 1, 1952, an electrocardiogram was obtained during an attack of anginal pain, which was associated with marked perspiration and weakness. In this tracing (Fig. 3, *B*) the R waves had disappeared in the Leads V_1 through V_3 and were rudimentary in Lead V_4. On that day the

hospital record stated: "Anteroseptal infarction definite now." However, when another electrocardiogram was taken two days later, (Fig. 3, *C*) it was noted that the R deflection had reappeared in the right-sided precordial leads and were even higher than previously in Leads V_3 and V_4. During January, 1952, the frequency and intensity of the anginal attacks gradually leveled off, and the patient was discharged greatly improved on Jan. 29, 1952.

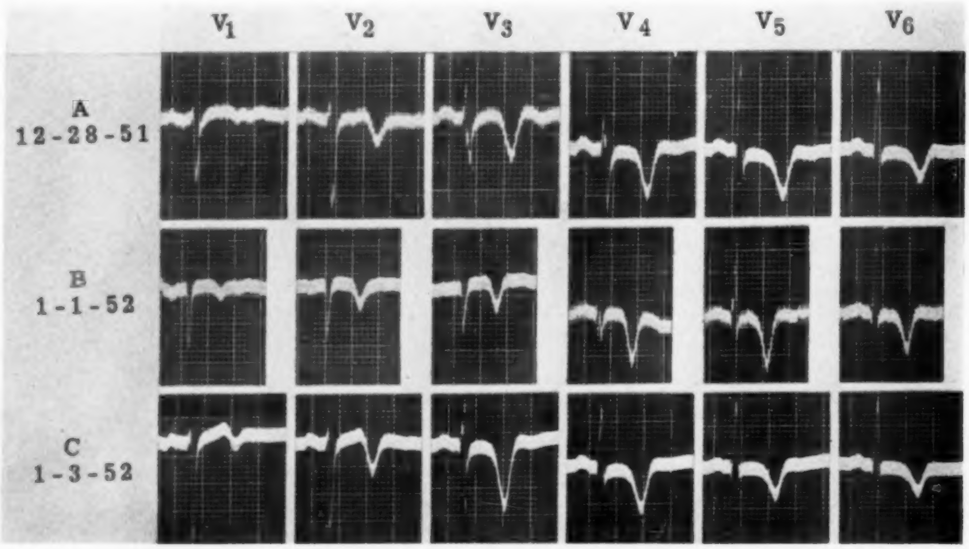

Fig. 3 (Case 2).—*A*, In all precordial leads except V_1 the T waves are sharply inverted. *B*, (During attack of severe anginal pain.) The R deflection has disappeared in V_1 through V_3 and is rudimentary in V_4. *C*, (Forty-eight hours after *B*.) The R deflection has returned in V_1 through V_4.

DISCUSSION

In the two patients reported here, marked reduction in the "coronary reserve" was suggested by sudden onset of angina of effort and frequent occurrence of anginal pain during rest, associated with alterations of the T wave in the electrocardiogram. A condition of this kind is often referred to as premonitory stage of myocardial infarction, although typical infarction follows only in a minority of cases. It did not develop in the patients of this report, although, judging from the increase of the sedimentation rate in both instances and transient low grade fever observed in Case 2, it may well be suspected that scattered areas of myocardial necrosis may have been present at one time or another during the long period of observation.

Electrocardiograms obtained during attacks of angina pectoris showed striking and unusual changes. The R wave disappeared in some of the precordial leads. In Case 1 significant elevation of the S-T junction was simultaneously present. These changes were transient. They lasted in Case 1 only for a few minutes, that is, for the duration of the anginal pain. In Case 2 the duration of the changes of QRS could not be exactly determined, because a follow-up tracing was not taken until 48 hours later, when reappearance of the R deflection was noted.

Attacks of angina pectoris, either spontaneous or induced by exercise, are often accompanied in the electrocardiogram by depression of the S-T segment and lowering or inversion of the T wave. In rare cases significant elevation of S-T develops,[8-15] apparently when the disturbance in the coronary circulation is of great magnitude.[8] In such instances electrocardiograms taken between attacks of angina pectoris often show alterations which suggest myocardial ischemia.[11] This was the case in the two patients of this report. Furthermore, we have often observed, as did others,[9,10,12,14] that transient coronary insufficiency superimposed on healed myocardial infarction causes reversal of inverted T waves and elevation of S-T, thus reproducing the features of acute myocardial infarction.

Wilson and associates made the statement that ". . . the diagnosis of myocardial infarction can be made with certainty from the electrocardiogram alone when characteristic changes of the QRS complex occur in association with RS-T displacement or typical changes of the T deflection."[7] The authors quoted an exceptional case in which changes of the QRS complex characteristic of myocardial infarction reverted after one month to normal. They suggested that in that particular instance ". . . the infarcted muscle was, for a time, incapable of responding to the excitatory process but it was not dead and subsequently recovered its excitability." Pronounced alterations in the QRS complexes, however, seldom disappear completely, but often undergo a very slow and much less pronounced regression.[7]

Levy and Hyman[15] reported an electrocardiogram (their Fig. 14) which showed in the precordial leads marked elevation of S-T and significant Q waves, diagnostic of anterolateral infarction. However, post-mortem examination including detailed microscopic study failed to show myocardial infarction, although it revealed the presence of stenosis of both coronary orifices. The authors thought that in rare instances the electrocardiogram may show the pattern of myocardial infarction, when the muscle fibers involved are severely injured, but did not suffer actual death, before the patient expired. Segers and associates[16] observed a patient who used to develop anginal pain after eating eggs. The electrocardiogram during the attack (their Fig. 5) showed in the precordial leads absence of R and inversion of the T wave. These changes, which reverted "soon" to normal, were attributed to an anaphylactic reaction that caused spasm of the coronary arteries. The same authors observed another patient suffering from angina pectoris, whose resting electrocardiogram (their Fig. 6) showed inversion of T in Leads I and V_4. Following exercise a wide, deep Q wave appeared in Lead V_4; it was no longer present in a tracing taken 4 days later.

In the two patients which we reported, significant changes of QRS accompanied attacks of angina pectoris and disappeared rapidly. In Case 1 the changes of QRS were associated with elevation of S-T. Both changes lasted only for a few minutes and were not followed by the development of classical clinical and electrocardiographic signs of myocardial infarction.

Thus, we are led to the conclusion, that transient coronary insufficiency, when it is of great magnitude, may produce not only temporary elevation of the S-T segment but also reversible changes of QRS, such as usually accompany extensive myocardial infarction.

SUMMARY

During spontaneous attacks of angina pectoris, which were observed in two patients, transient changes of the electrocardiogram occurred, such as are usually associated with myocardial infarction. The changes disappeared rapidly.

The electrocardiographic features usually held diagnostic of myocardial infarction, namely, significant Q deflections associated with elevation of the S-T segment or inversion of T, do not invariably represent dependable evidence of myocardial infarction. Transient coronary insufficiency, if it is of great magnitude, may in rare instances cause similar temporary changes of the electrocardiogram.

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THE DYNAMICS OF AORTIC VALVULAR DISEASE

HARRY GOLDBERG, M.D., ALVIN A. BAKST, M.D., AND CHARLES P. BAILEY, M.D.
PHILADELPHIA, PA.

INTRODUCTION

IN recent years the circulatory dynamics of acquired and congenital heart disease has been the subject of intensive study. This is largely due to the development of newer techniques for the study of the circulation in man and to the advances made in the surgical treatment of valvular deformities[1-6] and cardiac malformations.[7-11] Consequently, the effects of these lesions upon the circulation in man have been investigated.[12-25]

Our present knowledge of the pathologic physiology of aortic valvular disease is based largely upon experimental work.[26] Few measurements using the newer techniques have been made in patients with deformities predominantly of the aortic valve. Such a study is important in that it provides a better understanding of the effects of these lesions and serves as a basis for the evaluation of surgical measures employed in their treatment. The present report deals with the altered circulatory patterns in patients with aortic valvular disease at rest and during exercise. Many of the patients studied herein have had definitive treatment for aortic stenosis according to the technique described by Larzelere and Bailey.[27] The hemodynamic changes following surgery in these patients will be the subject of a subsequent communication.[28]

MATERIAL

Forty patients with aortic valvular disease were studied. The clinical data appear in Table I. Aortic stenosis was the predominant deformity with respect to the aortic valve in twenty-six patients. This constitutes Group A. In all cases of this group the diagnosis was confirmed at surgery. In eleven cases neither stenosis nor regurgitation was felt on digital exploration of the mitral valve by the surgeon (C.P.B.). Findings preoperatively and at surgery did not suggest mitral valve involvement in an additional seven cases, and hence the valve was not explored. In these eighteen cases the only lesion significant physiologically was aortic stenosis. These individuals will be referred to as having "pure"*

From the B'rith Sholom Laboratory for Cardiovascular and Pulmonary Research, and the Departments of Physiology and Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pa.

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*Although some aortic regurgitation may have been present and though the mitral valve may not have been free of histologic evidence of rheumatic fever, from a physiologic point of view these lesions were not significant.

TABLE IA. CLINICAL DATA: AORTIC STENOSIS PREDOMINANT LESION

CASE	AGE	SEX	SYMPTOMS					PHYSICAL EXAMINATION						RHYTHM	SIGNS OF CONG. FAILURE	ECG	ROENTGENOGRAPHY AND FLUOROSCOPY		HISTORY OF RHEUMATIC FEVER
								AORTIC AREA				APICAL AREA							
			CHEST PAIN	DIZZINESS (d) SYNCOPE (s)	DYSPNEA	FATIGUE	OTHER	THRILL	MURMUR		SECOND SOUND	MURMUR					CHAMBER ENLARGEMENT	CALCIF. AORTIC VALVE	
									SYST.	DIAST.		SYST.	MID-LATE OR PRE-SYST.						
E.C.	43	M	0	s	E, Or, PN	+	Palp. Convulsions	0	3+	+	D	2+	0	AF	0	LHS Dig	LV 2-3+ LA 1+ RV 1+	+	+
R.C.	33	M	0	d	E, PN	0	0	0	2+	+	I	2+	0	R	0	LHS	LV 2+ LA 1+	0	+
W.C.	33	M	+	d, s	E, Or	+	0	+	4+	+	0	3+	0	R	0	LHS	LV 3+ LA 1+	0*	0
M.C.	40	F	0	0	E	0	Pulm. edema Hemop.	0	1-2+	+	D	3+	+	R	0	Dig	LA 3+ RV 1+ LV 1+	0	0
A.C.	56	M	0	s	E	0	0	+	3+	0	D	2+	0	R	Few râles LLL	LHS Dig	LV 1-2+	+	0
W.E.	16	M	0	0	E	+	Palp.	+	3+	0	N	0	0	R	0	LHS early	0	+	Murmur since age 1

W.Er.	36	M	+	0	PN	0	0	+	3+	0	D	2+	+	R	0	WNL	0	0	0
W.I.	28	M	+	s	0	0	Palp.	+	3+	+	0	0	0	R	0	LHS	LV 1+	0*	0
F.K.	35	M	+	0	E	+	0	+	4+	+	D	2+	0	R	0	LHS	LV 2+ LA 1+	+	0
P.K.	43	M	+	d	Or	0	Palp. Hemop.	+	4+	+	0	2+	0	R	0	LHS	LV 1-2+	+	0
F.M.	30	M	+	0	E	0	Palp.	+	3+	0	D	2+	0	R	0	LHS	LV 1+	0	0
R.N.	30	M	+	d, s	E	+	Hemop.	+	3+	0	D	2+	0	R	0	LHS	0	+	+
L.R.	(0	M	0	0	E, Or, PN	+	Hemop.	0	2-3+	0	D	0	0	R	0	LHS	LV 1+ LA 1-2+	0*	0
E.Sch.	35	M	+	0	E	0	Palp. Hemop.	+	4+	+	0	2+	+	R	0	LBBB	LV 2+ LA 1-2+	0	0
J.B.	35	M	0	0	E	+	0	+	3+	0	0	0	0	R	0	LBBB	LV 3+	+	Murmur since age 3 mo.
J.S.	43	M	0	0	E	+	0	+	3+	0	D	2+	0	R	0	LBBB	LV 2+ LA 2+	+	+
E. Seg.	51	F	+	0	E, Or	+	Palp.	+	4+	+	0	3+	+	R	0	LHS	LV 2+ LA 1-2+ RV 1+	+	+
S.T.	39	M	0	d	E	0	0	+	3+	0	D	3+	0	R	0	LHS	0	+	Murmur since age 3
J.U.	45	M	0	0	E, Or	0	0	+	3+	+	D	0	0	R	0	LHS	LV 0-1+	+	0

Table IA. Clinical Data: Aortic Stenosis Predominant Lesion (Continued)

CASE	AGE	SEX	SYMPTOMS					PHYSICAL EXAMINATION						RHYTHM	SIGNS OF CONG. FAILURE	ECG	ROENTGENOGRAPHY AND FLUOROSCOPY		HISTORY OF RHEUMATIC FEVER
								AORTIC AREA				APICAL AREA							
									MURMUR			MURMUR							
			CHEST PAIN	DIZZINESS (d) SYNCOPE (s)	DYSPNEA	FATIGUE	OTHER	THRILL	SYST.	DIAST.	SECOND SOUND	SYST.	MID-LATE OR PRE-SYST.				CHAMBER ENLARGEMENT	CALCIF. AORTIC VALVE	
W.W.	31	M	+	0	E	0	0	+	3-4 +	+	D	2 +	0	R	0	LHS	LV 2 +	+	0
A.G.	41	M	0	0	E	0	Palp. Cerebral Embol.	0	2 +	+	N	3 +	+	R	0	Dig.	RV 1 + LA 3 + LV 1 +	0	0
W.D.	36	M	+	0	E, PN	0	Hemop.	+	4 +	+	0	2 +	0	R	0	LHS	LV 1-2 + LA 1 +	+	+
I.B.	42	F	0	0	E	+	Palp.	+	3 +	+	0	3 +	+	AF	0	AF Dig	LV 1 + LA 1 + RV 2 +	0	+
R.G.	27	F	+	d	E, PN	0	Cough Palp.	0	2 +	0	I	0	+	R	0	WNL	LV 1 + RV 1 + LA 2 +	+	+
W.H.	49	M	+	s	E, PN, Or	+	0	+	3 +	+	0	2 +	0	R	0	LHS	LV 1-2 + LA 0-1 +	+	0
D.R.	49	M	0	0	E, Or	+	Hemop.	+	4 +	+	D	2 +	0	R	0	LHS	LV 2 + LA 2 +	+	0

For key see Table IB.

aortic stenosis. In the latter group, aortic regurgitation was absent clinically in thirteen, minimal in six, and moderate in one. The mitral valve was involved in six patients of Group A. Four patients had mitral stenosis with either minimal or no regurgitation; two had mitral stenosis with regurgitation of physiologic significance. In one case (J.S.), there was minimal insufficiency of the mitral valve which may have been due more to dilatation of the mitral ring rather than to intrinsic disease of the valve. In this group with coexisting mitral valvular disease, aortic stenosis was the predominant lesion in all but three cases (M.C., A.G., and R.G.). In the latter, the principle lesion was mitral stenosis with aortic stenosis, moderate in severity in two (A.G. and R.G.), and minimal in one (M.C.). In one patient (R.G.), the diagnosis of minimal tricuspid stenosis was confirmed at surgery.

Group B consisted of fourteen patients in whom aortic regurgitation was the predominant lesion. The mitral valve was normal in eight cases. In two additional cases the mitral valve was not explored since the findings at surgery did not suggest the presence of mitral valvular disease. There was minimal mitral regurgitation in one patient. In eleven patients subjected to surgery aortic stenosis was minimal. In the twelfth (G.W.), the stenosis was of moderate degree. Two individuals in this group (P.W. and S.L.) were not operated upon. Since their clinical findings were classical for aortic regurgitation, they were included in this series.

A definite history of rheumatic fever was present in only five patients in Group A, and in twelve in Group B. However, rheumatic fever was considered to be the etiology of the valvular deformities in all cases except four (S.T., W.E., J.B., and L.R.). In these four individuals the aortic valve alone was involved. In one (L.R.), aged 60, atherosclerosis may have been a factor. In the other three who gave a history of the presence of a murmur since the age of three months, one year, and three years, respectively, the probability of a congenital etiology was entertained, although rheumatic fever could not be entirely eliminated.

METHODS

All patients were studied in the postabsorptive state by right heart catheterization. No sedation was given immediately prior to the procedure. The catheter was passed into the pulmonary artery. In some cases, "pulmonary venous capillary" pressures and samples were obtained.[29] After withdrawal of the catheter until the tip lay in the main pulmonary artery, a Cournand needle was introduced into the brachial artery. When the patient's pulse and respiration became stabilized the resting cardiac output was obtained. Expired air was collected for a three-minute period in a Tissot Spirometer. Samples of blood were obtained simultaneously from the pulmonary and brachial arteries midway during collection of the resting gas sample. Resting pulmonary and brachial arterial pressures were obtained at this time. The parients then exercised in the recumbent position for a three-minute period by raising two one-pound weights, a weight being tied

TABLE IB. CLINICAL DATA: AORTIC REGURGITATION PREDOMINANT LESION

CASE	AGE	SEX	SYMPTOMS					PHYSICAL EXAMINATION						RHYTHM	SIGNS OF CONG. FAILURE	ECG	ROENTGENOGRAPHY AND FLUOROSCOPY		HISTORY OF RHEUMATIC FEVER
								AORTIC AREA				APICAL AREA							
									MURMUR			MURMUR							
			CHEST PAIN	DIZZINESS (d) SYNCOPE (s)	DYSPNEA	FATIGUE	OTHER	THRILL	SYST.	DIAST.	SECOND SOUND	SYST.	MID-LATE OR PRESYST.				CHAMBER ENLARGEMENT	CALCIF. AORTIC VALVE	
T.V.	33	M	+	d	PN, Or	0	0	Faint	2+	+	I	2+	+	R	0	LHS	LV 3+ LA 1+	0	+
R.B.	20	M	0	0	0	0	Palp.	0	3+	+	N	2+	+	R	0	LHS	LV 1-2+	0	+
F.B.	27	M	+	d	E, PN	+	Hemop.	+	4+	+	D	3+	0	R	0	LHS	RV 2+ LV 3+ LA 2+	0	+
S.B.	34	M	+	0	E	+	0	+	2+	+	D	0	0	R	0	LHS	LV 2+ LA 1+ RV 0-1+	0	+
A.M.	30	M	+	d	E	+	Palp.	0	3+	+	D	0	0	R	0	LHS	LV 2+	0	+
H.M.	42	M	0	0	E	+	0	0	3+	+	D	0	+	R	0	LHS	LV 2+	0	+
M.R.	12	F	0	0	E	0	0	0	2+	+	N	0	0	R	0	LHS	LV 1+	0	+
J.R.	26	M	0	0	E	0	0	0	2+	+	N	2+	0	R	0	RBBB	LV 3+ LA 1+	0	+

E.Mc.	49	F	+	0	E, Or	+	0	0	2+	+	N	2+	0	R	0	ST dep. in V_5 V_6	LV 2+	0	0
W.O.	25	M	+	0	E	0	Palp.	+	3+	+	D	2+	0	R	0	LHS	LV 2+	+	+
S.C.	18	M	+	d, s	E, Or	+	0	0	2+	+	N	4+	0	R	0	LHS	LV 2+ LA 1+	0	+
P.W.	15	F	0	0	E	+	Palp.	+	3-4+	+	0	2+	+	R	0	LHS	LA 2+ LV 2-3+ RV 1+	0	+
S.L.	24	M	+	s, d	E	+	0	0	?	+	0	0	0	R	0		LV 2+	0	+
G.W.	45	M	+	0	E, PN Or	+	Periph. Edema	+	0	+	0	3+	0	R	0	LHS	LV 2+ LA 3+ RV 1+	0	+

KEY

+: Present
O: Absent
E: Exertional
Or: Orthopnea
PN: Paroxysmal nocturnal dyspnea
D: Diminished
Palp.: Palpitation
Hemop: Hemoptysis
I: Increased
N: Normal
AF: Auricular fibrillation
R: Regular

WNL: Within normal limits
Dig: Digitalis effect
LHS: Left heart strain
LBBB: Left bundle branch system block
RBBB: Right bundle branch system block
*: Calcification found at surgery
LV: Left ventricle
RV: Right ventricle
LA: Left atrium

to each leg. In order to minimize the sources of error in obtaining a "steady state" during short periods of exercise the following were done: (1) the height to which each leg was flexed was fixed, allowing the one-pound weight to be raised only one foot; (2) each leg was raised thirty times per minute, this rhythm being accomplished with the aid of a member of the catheterization team; and (3) simultaneous samples of blood from the pulmonary artery and brachial artery and expired gas samples were obtained during the last minute of exercise to calculate the "exercise cardiac output." It was noted that the effect of exercise upon the pulmonary arterial pressure, the arteriovenous oxygen difference, and the cardiac output are similar whether the exercise period was three or five minutes. Our experience in other valvular deformities, such as mitral stenosis and regurgitation,[21,31] and the experience of others,[19] with results from the use of three- or five-minute exercise periods are similar to those obtained with longer exercise periods.[24]

The zero level for all pressures was taken as five centimeters below the angle of Louis. Pressures were measured with a capacitance-type electromanometer* with recordings on the direct-writing polyoscillograph.* Mean pressures were obtained by electrical integration. The pressure recordings were calibrated with a mercury manometer.

Blood samples were analyzed for oxygen content and capacity according to the method of Van Slyke and Neill.[32] The oxygen content of expired air was analyzed on the Pauling analyzer and 0.5 c.c. Scholander gas analyzer. The volume was expressed as dry gas at 0° centigrade and 760 mm. Hg. Cardiac outputs were calculated by the direct Fick method. Pulmonary arteriolar resistance and work done by the right ventricle were determined by the method of Gorlin and Gorlin.[33]

After the right heart catheterization, when the resting state had been resumed, continuous brachial arterial pressure recordings were made through the Cournand needle during the Valsalva maneuver. In the recumbent position the patient was encouraged to strain against a closed glottis for approximately 15 seconds. Simultaneous recordings of the brachial arterial pressure and the electrocardiogram were made until control conditions were reached following the straining maneuver.

RESULTS

Group A.—The physiologic data obtained in this group are shown in Table IIA. The oxygen consumption ranged between 86 and 186 c.c./min./M.[2] In three patients (M.C., A.C., and J.U.) the value fell below 100, while in three others it was above 170. The resting cardiac index ranged between 1.6 and 4.0, averaging 2.2 L./min./M.[2] for the entire group. It was within normal limits in eleven, lowered in eleven, and elevated in four. Of those eleven patients with a low cardiac index at rest, the oxygen consumption was slightly low in three, but

*Sanborn Company.

not significantly in two (A.C. and J.U.). Three patients (E.C., M.C., and D.R.) with coexisting mitral valvular disease fell into the group with low cardiac indices. Of the four patients with a resting cardiac index above normal, three had coexisting mitral valvular disease. The resting pulse rate was generally within the normal range, being elevated in only three patients (R.G., E.S., and W.C.). Consequently, the stroke index, in general, varied directly with the cardiac index.

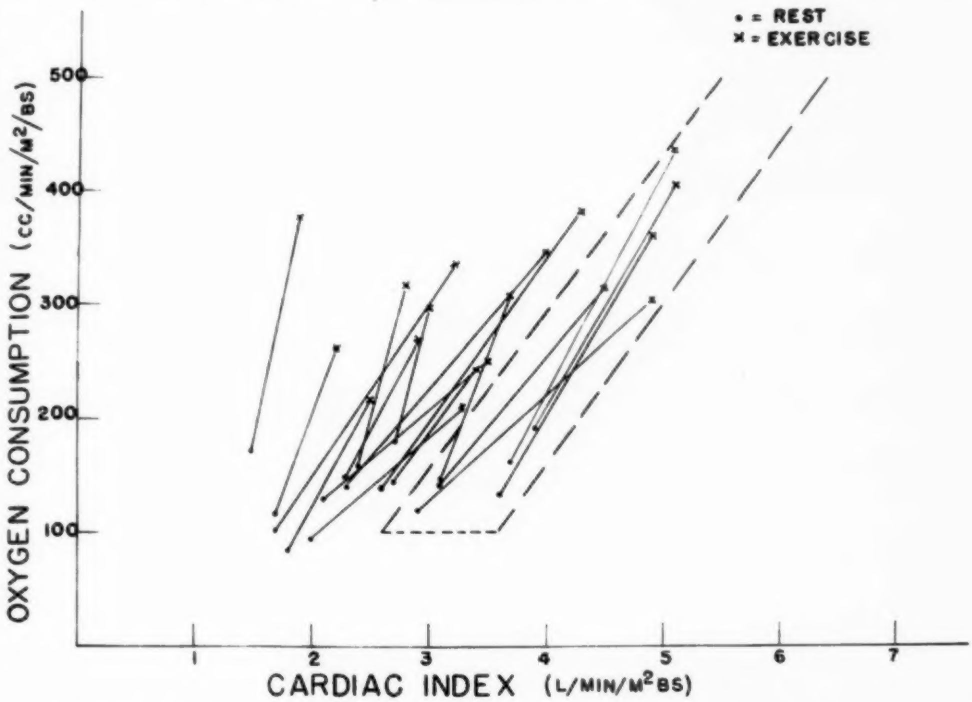


Fig. 1.—The relationship of the oxygen consumption and cardiac index at rest and during exercise in eighteen patients with aortic stenosis. The area enclosed by the broken lines represents the normal values at rest and during exercise as determined in normal individuals.[30,35,53]

The arteriovenous oxygen difference was within the normal limits for all but ten patients during the resting state. In all but two of the latter, the cardiac index was below normal.

During exercise the oxygen consumption ranged between 217 and 438 c.c./min./M.^{2}, 1.7 to 3.2 times the resting values. The increase in oxygen consumption during exercise was used as a measure of the work performed.

There was a rise in the cardiac output during exercise in all patients, 18 in number, in whom this determination was made. In thirteen patients, the response to exercise was less than would be expected when compared with the normal. Hence, in Fig. 1 the slope of the line connecting the resting and exercise $\frac{O_2 \text{ consumption}}{\text{cardiac index}}$ ratio is steeper in these patients than in the normal represented by the slope of the enclosed area. Of these patients with an inadequate rise in

Table IIA. Physiologic Data: Aortic Stenosis Predominant Lesion

Cases	O_2 Cons. c.c./min./M^2		A-V O_2 Diff. Vol. (%)		Cardiac Output L./min.		Cardiac Index L./min./M^2BS		Pulse Rate		Stroke Index		Pulmonic Circulation: PA Press. (Mean) mm. Hg		Pulmonic Circulation: RV Press. S/D mm. Hg	Pulmonic Circulation: RA Press. mm. Hg	Pulmonic Circulation: PVC Press. mm. Hg	Pulmonic Circulation: PA Resist. Dynes sec. cm.$^{-5}$	Pulmonic Circulation: RV Work Kg./min./M^2	Systemic Circulation: Press. S/D mm. Hg	Systemic Circulation: Pulse Press.	Systemic Circulation: Peak of Systole sec.	BA O_2 Sat. (%)	
	R	E	R	E	R	E	R	E	R	E	R	E	R	E									R	E
E. C.	119	260	6.8	11.6	3.7	4.8	1.7	2.2	80	112	21	20	(30)	(50)	—	—	16	304	—	110/49	61	a) 0.12 b) 0.20	90	90
R.C.	147	309	4.6	8.4	5.6	6.7	3.1	3.7	71	88	44	42	(12)	(24)	15-19/0-4	1	4	118	0.45	112/54	58	0.23	92	94
W.C.	159	318	7.0	11.4	4.0	4.7	2.4	2.8	100	125	24	22	(37)	(44)	50-55/5	0	16	421	1.26	90/64	26	0.25	90	90
M.C.	86	217	4.8	8.8	2.6	3.6	1.8	2.5	85	101	21	25	(29)	(41)	44-46/−2	−2	14	462	0.80	97/54	43	0.08	90	98
A.C.	97	—	6.1	—	3.0	—	1.58	—	71	—	23	—	(27)	—	34-41/0	2	7	530	0.57	92/50	42	0.24	92	—
W.E.	122	—	4.1	—	4.6	—	2.9	—	87	—	33	—	(10)	—	19-24/2	3	6	70	0.29	85/67	18	0.20	92	—
W.Er.	103	334	4.5	8.0	4.7	8.6	1.7	3.2	75	80	23	40	(6)	(10)	14-16/−2	0	2	68	0.14	132/80	52	0.21	94	92
W.I.	141	316	4.5	7.0	5.9	8.6	3.1	4.5	80	91	39	49	(18)	(18)	30/0-2	−2	6	163	0.89	97/58	39	0.26	92	93

F.K.	192	405	4.9	8.0	7.0	9,0	3.9	5.1	79	106	49	48	(21)	(40)	42-45 / 2	2	11	115	1.06	110 / 48	62	0.23	97	92
P.K.	144	242	5.3	7.0	5.0	6.3	2.7	3.4	70	94	39	36	(13)	(21)	26-30 / —4	—4	5	128	0.66	102 / 50	52	0.26	94	92
F.M.	120	304	4.2	6.2	5.9	10.1	2.9	4.9	84	106	35	46	(17)	(26)	—	—	9	108	—	104 / 64	40	0.24	93	96
R.N.	134	360	4.9	7.4	7.1	9.6	3.6	4.9	86	120	42	41	(18)	(22)	—	4	8	113	0.72	102 / 64	38	0.23	96	97
L.R.	129	—	8.1	—	2.7	—	1.6	—	71	—	23	—	(25)	—	38-44 / —4-0	—2	8	504	0.62	114 / 40	74	0.23	97	—
E.Sch.	139	381	5.1	8.8	5.6	9.1	2.6	4.3	55	97	47	44	(26)	(46)	45-50 / 2	0	15	157	0.97	104 / 44	60	0.26	89	92
J.B.	173	378	6.4	12.4	5.34	6.01	1.52	1.85	85	108	18	18	(20)	(34)	—	—	—	—	—	128 / 99	29	0.09	89	90
J.S.	167	—	6.5	—	4.8	—	2.6	—	61	—	43	—	** 17-20 / 6-8	—	30 / 0	0	—	—	—	126 / 70	56	0.23	98	—
E.Seg.	163	—	5.1	—	4.4	—	3.2	—	100	—	32	—	(39)	—	40-62 / 5	0	13	473	0.52	100 / 40	60	0.20	90	—
S.T.	136	—	4.7	—	4.6	—	2.6	—	66	—	39	—	(14)	—	14-20 / 0-2	0	5	157	0.52	105 / 60	45	0.22	92	—
J. U.	96	209	5.1	6.2	4.8	7.9	2.0	3.3	86	92	23	36	(15)	(21)	22-36 / 2	3	—	—	0.35	93 / 58	40	0.27	96	94

TABLE IIA. PHYSIOLOGIC DATA: AORTIC STENOSIS PREDOMINANT LESION (CONTINUED)

CASES	O_2 CONS. C.C./MIN./M^2		A-V O_2 DIFF. VOL. (%)		CARDIAC OUTPUT L./MIN.		CARDIAC INDEX L./MIN./M^2BS		PULSE RATE		STROKE INDEX		PULMONIC CIRCULATION: PA PRESS. (MEAN) MM. HG		PULMONIC CIRCULATION: RV PRESS. S/D MM. HG	PULMONIC CIRCULATION: RA PRESS. MM. HG	PULMONIC CIRCULATION: PVC PRESS MM. HG	PULMONIC CIRCULATION: PA RESIST. DYNES SEC. CM.$^{-5}$	PULMONIC CIRCULATION: RV WORK KG./MIN./M^2	SYSTEMIC CIRCULATION: PRESS. S/D MM. HG	SYSTEMIC CIRCULATION: PULSE PRESS.	SYSTEMIC CIRCULATION: PEAK OF SYSTOLE SEC.	BA O_2 SAT. (%)	
	R	E	R	E	R	E	R	E	R	E	R	E	R	E									R	E
W.W.	140	345	6.1	8.6	4.1	7.1	2.3	4.0	72	86	32	47	(16)	(16)	19/0	0	4	234	0.53	110/60	50	0.27	95	93
A.G.	140	—	4.2	—	5.6	—	4.0	—	74	—	56	—	(25)	—	39/0-2	4	12	158	1.20	104/60 88/70	44 18	0.10 0.07	89	—
W.D.	161	438	4.3	8.7	7.4	10.0	3.7	5.1	94	116	39	44	(20)	(38)	26-32/2	5	11	97	0.80	96/54	42	0.22	96	93
I.B.	180	298	6.7	10.0	4.2	4.7	2.7	3.0	86	89	31	34	** 58-67/17-27	—	52-64/10	9	12	—	—	134/55 108/82	79 46	0.24 0.12	88	97
R.G.	186	—	4.0	—	6.2	—	4.0	—	100	122	40	—	(21)	(33)	31/3	5	—	—	0.92	130/70	60	0.11	92	—
W.H.	149	268	6.5	9.0	4.1	5.2	2.3	2.9	72	90	32	32	(25)	(34)	32-35/—2-0	1	9	313	0.79	102/40	62	0.22	97	97
D.R.	131	350	6.1	10.0	3.6	6.0	2.1	3.5	66	80	32	31	(10)	(20)	22-30/0-2	—2	9	22	0.36	110/42	68	0.22	91	98

**Systolic/Diastolic

the cardiac output, three had mitral valvular disease. Since the blood flow was inadequate to meet the tissue oxygen demands, the extraction of oxygen by the tissues, as measured by the arteriovenous oxygen difference, was increased. Fig. 2 shows the relationships of the oxygen consumption and the arteriovenous oxygen difference. The latter was abnormally increased in seven patients at rest, while during exercise twelve demonstrated an increased oxygen extraction from the tissues.

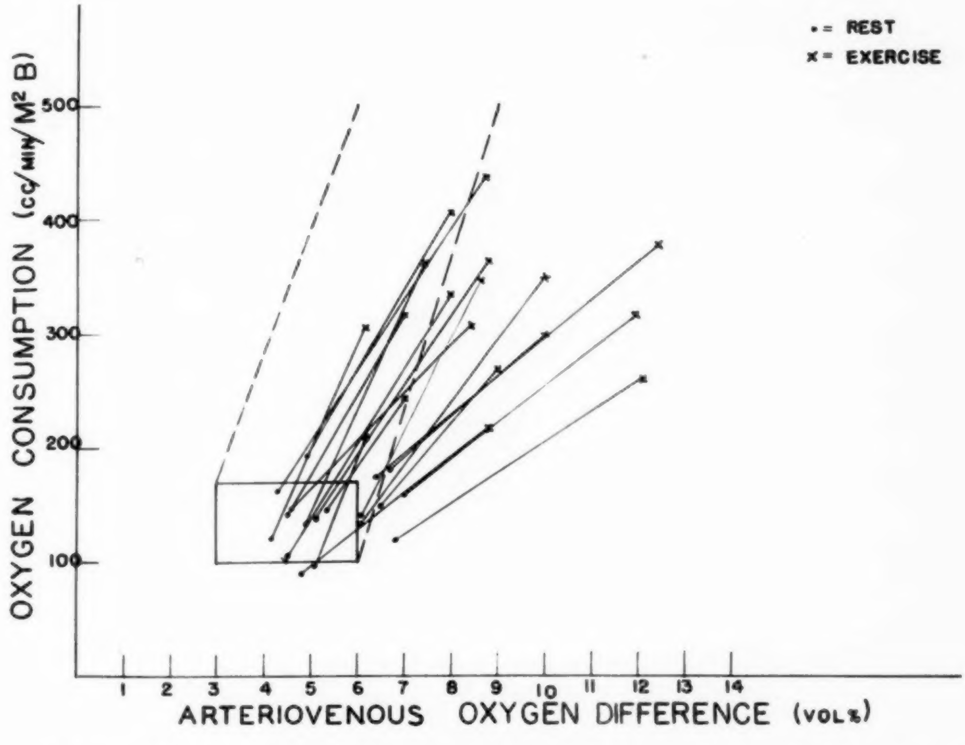


Fig. 2.—The relationship of the oxygen consumption and arteriovenous oxygen difference at rest and during exercise in eighteen patients with aortic stenosis. The area enclosed by the rectangle and the straight lines extending from its extremities represent the range of normal values.[30,35,53]

The mean pulmonary arterial pressures were normal at rest in twelve patients, and elevated in fourteen (Table IIA). Of the latter, five had mitral valvular disease (R.G., M.C., A.G., F.K., and E.C.). Of the remaining nine patients with pulmonary hypertension, the "pulmonary venous capillary" pressure was normal in four (W.H., I.B., L.R., and A.C.), and elevated in three (W.C., E.Sch., and E.Seg.).

Resting "pulmonary venous capillary" pressures were obtained in all but six patients. They were found to be elevated in five, two of whom had mitral valvular disease (E.C. and M.C.). Three patients in whom the mitral valve was physiologically normal, had resting "pulmonary venous capillary" and pulmonary arterial hypertension.

The effect of exercise upon the pulmonary circulation was obtained in eighteen patients (Fig. 3). In ten of these patients the resting pulmonary arterial pressure was within normal limits and remained so in six. Four individuals developed pulmonary hypertension during exercise. In the remaining eight patients the pulmonary arterial pressure was elevated at rest and rose further during exercise. It is to be noted that all patients with coexisting mitral stenosis

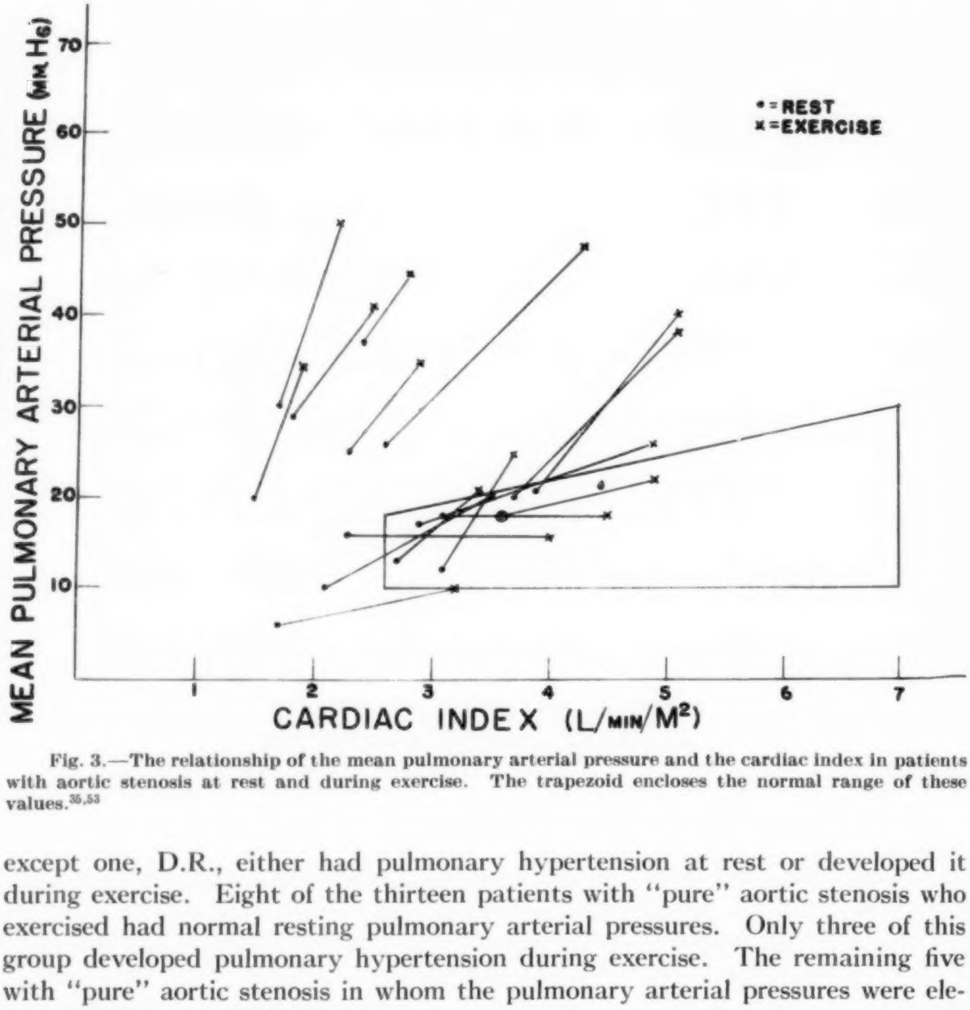


Fig. 3.—The relationship of the mean pulmonary arterial pressure and the cardiac index in patients with aortic stenosis at rest and during exercise. The trapezoid encloses the normal range of these values.[35,53]

except one, D.R., either had pulmonary hypertension at rest or developed it during exercise. Eight of the thirteen patients with "pure" aortic stenosis who exercised had normal resting pulmonary arterial pressures. Only three of this group developed pulmonary hypertension during exercise. The remaining five with "pure" aortic stenosis in whom the pulmonary arterial pressures were elevated at rest rose still higher.

Calculations of the pulmonary arteriolar resistance were made in seventeen patients with "pure" aortic stenosis. It was within normal limits in four, slightly elevated in eight, and moderately elevated in five (W.H., W.C., A.C., L.R., and E.Seg.). It was generally above normal in patients who had coexisting mitral valvular disease.

Right ventricular work was within normal limits except for three patients (W.C., A.G., and F.K.), two of whom had coexisting mitral valvular disease.

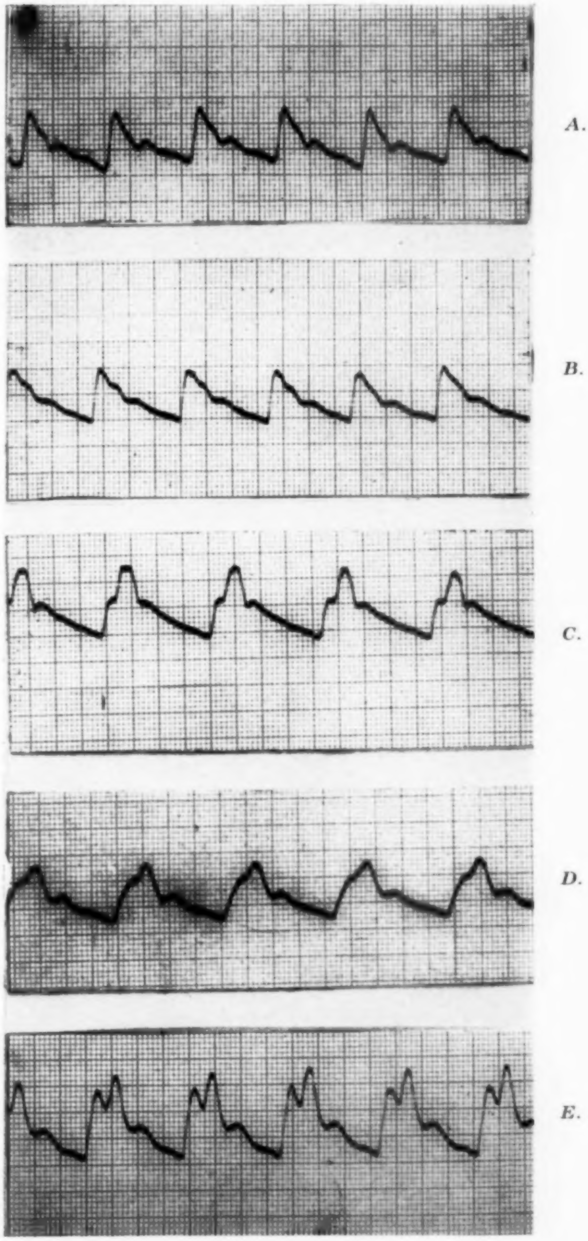


Fig. 4.—Brachial arterial pressure curves. *A*, From a normal individual; *B*, *C*, *D*, *E*, From patients with aortic stenosis; *B*, Mild degree (patient M.C.). Note slight notch on catacrotic limb between peak of systole and dicrotic incisura. *C* (patient W.Er.) and *D* (patient S.T.), Anacrotic phenomenon. *E*, Double-summit type (patient F.K.).

Evidence for the existence of right ventricular failure was present at rest in one patient (R.G.) in whom the end-diastolic pressure in the right ventricle was 10 mm. Hg. Right ventricular pressures were not recorded during exercise in this group.

Brachial arterial pressure curves were obtained in all patients. The pulse pressure ranged between 18 and 79 mm. Hg, the majority falling within the normal range. In no case was the brachial arterial pressure curve perfectly normal in contour. An interruption of the upstroke (anacrotic limb) was found in eighteen patients (Fig. 4). In eleven of these there was a distinct notch (anacrotic notch). In the remaining seven the interruption appeared as a break or "slur" in the anacrotic limb with a subsequent slow rise in the curve to the peak of systole.

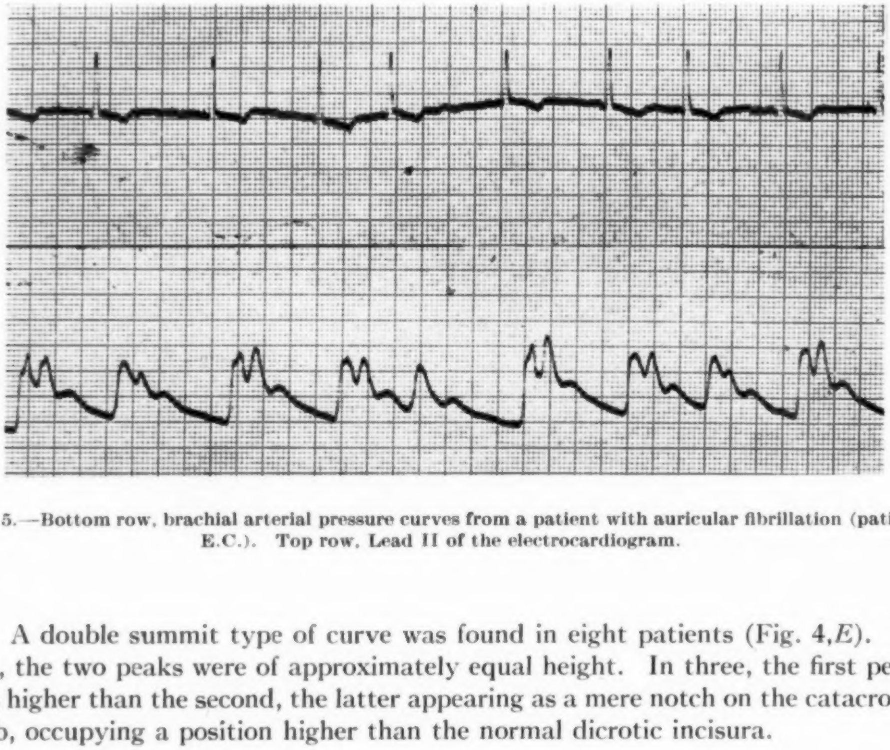


Fig. 5.—Bottom row, brachial arterial pressure curves from a patient with auricular fibrillation (patient E.C.). Top row, Lead II of the electrocardiogram.

A double summit type of curve was found in eight patients (Fig. 4,*E*). In five, the two peaks were of approximately equal height. In three, the first peak was higher than the second, the latter appearing as a mere notch on the catacrotic limb, occupying a position higher than the normal dicrotic incisura.

In one case (W.E.) the anacrotic notch in the brachial arterial pressure curve was followed by multiple notches up to the peak of systole. In this individual, a pressure tracing of the ascending aorta, made through a No. 5F catheter, was similar in contour. In all other instances, the anacrotic notch was followed by a smooth curve. Marked variation in the pressure pulse contour was observed in those patients with auricular fibrillation (E.C., A.G., and I.B., see Fig. 5). In all but one case, (W.H.), the dicrotic incisura was distinctly present. This patient was the only one in Group A who had a moderate degree of aortic regurgitation.

In all cases in which an interruption in the anacrotic limb occurred, either by a true notch or a mere slur, the peak of systole was delayed. In a group of ten normal individuals the onset of the peak of systole from the beginning of the rise of the brachial arterial pressure curve ranged between 0.06 and 0.09 sec., averaging 0.08 sec. In the patients with aortic stenosis and in those with an anacrotic pulse, the peak of systole ranged from 0.20 to 0.27 sec., averaging 0.23 sec. In those cases with double-peaked curves the first peak ranged from 0.08 to 0.13 sec., averaging 0.10 sec., and the second peak ranged from 0.16 to 0.25 sec., averaging 0.21 sec.

The effect of the Valsalva maneuver upon the brachial arterial pressure curve was determined in sixteen patients. Marked changes in the contour of the curve were observed during and immediately following the straining period. In general, when the strain was sufficiently intense, the anacrotic notch or the double-summit type of pressure curve was replaced by a smooth curve during the straining period when the pulse pressure was small. In the poststraining period, the anacrotic or double-summit curve gradually reappeared. In the presence of an overshoot in the blood pressure, with an increase in the pulse pressure, a double-summit type of curve was converted into an anacrotic pulse. Similarly, a pre-existing anacrotic notch assumed a lower position on the upstroke in those complexes in which the pulse pressures were greater than in the control (Fig. 6). An overshoot in the blood pressure in the poststraining period was obtained in the majority of the patients. It is of interest that in those individuals with the double-summit type of curve in whom the first peak was greater than the second peak and who responded to the Valsalva maneuver with an overshoot in the blood pressure, the anacrotic notch in the large complexes in the post-straining period corresponded to the first peak in the resting pressure tracing. Similarly, the peak of systole during this period corresponded to the second peak in the control tracing.

Group B.—The physiologic data obtained in this group are shown in Table IIB. In general, the results are similar. The oxygen consumption ranged between 96 and 162 c.c./min./M.^{2}, being below 100 in only one patient (H.M.). The resting cardiac index obtained in twelve cases ranged from 1.9 to 3.7 with an average of 2.8 L./min./M.^{2} It was below the lower limits of normal in only four patients, in one of whom the oxygen consumption was the lowest of the entire group (H.M.). In a second (G.W.) a minimal degree of mitral regurgitation was found. In the other two patients the mitral valve was felt to be normal by the surgeon (C.P.B.).

The arteriovenous oxygen difference in these patients was within the normal range for all but one. This patient (G.W.) with a low cardiac output, had a widened arteriovenous oxygen difference.

During exercise the oxygen consumption ranged between 210 and 418 c.c./min./M.^{2}, 1.6 to 2.6 times the resting values. The "exercise cardiac index" obtained in ten patients rose in all but two (A.M. and J.R.). In one-half of the

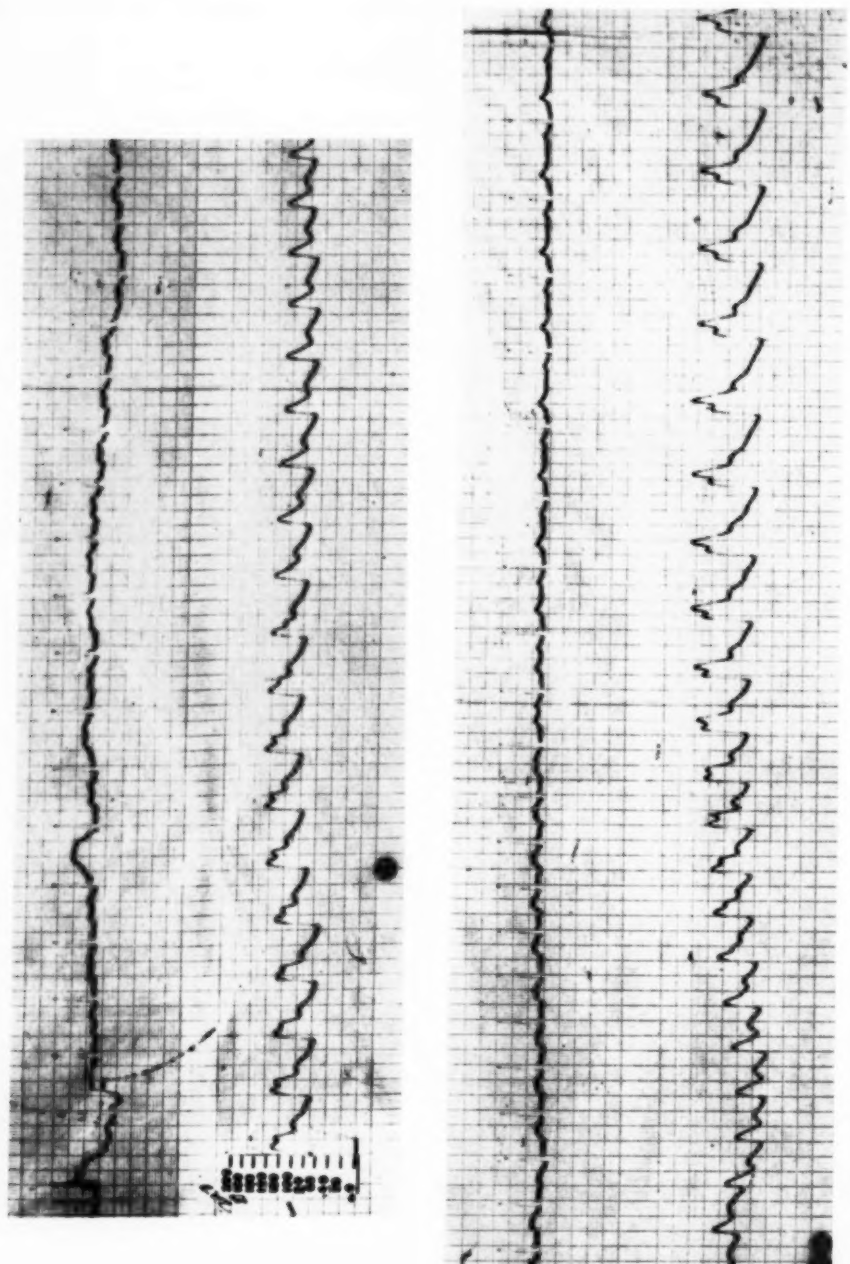


Fig. 6.—Continuous recording of the brachial arterial pressure during and immediately following the Valsalva maneuver (bottom row). (.) represents beginning of strain. (. .) represents release of strain. Top row. Lead II of the electrocardiogram.

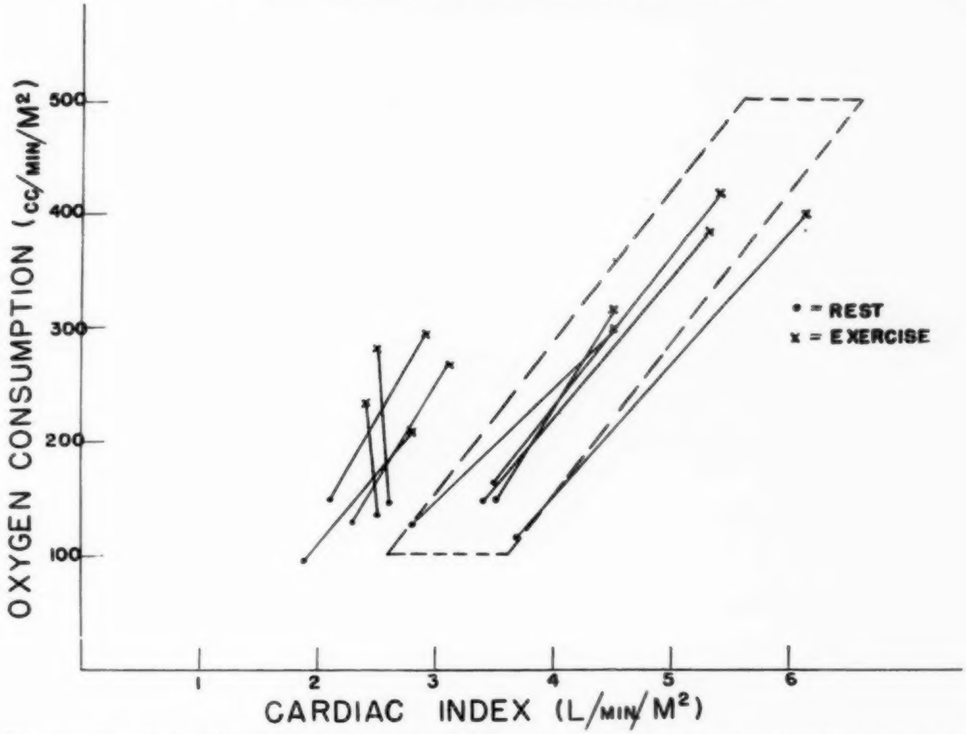


Fig. 7.—The relationship of the oxygen consumption and cardiac index at rest and during exercise in ten patients with aortic regurgitation. Conventions as in Fig. 1.

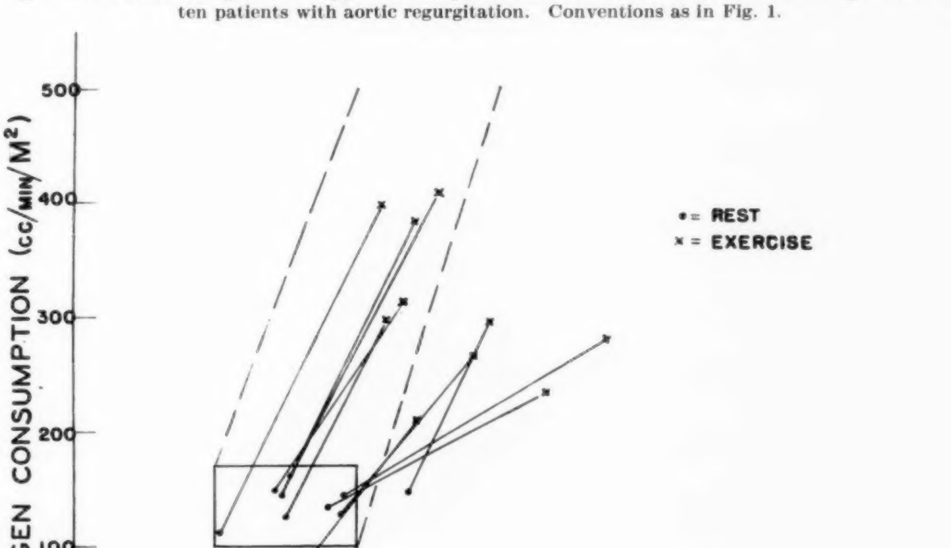


Fig. 8.—The relationship of the oxygen consumption and arteriovenous oxygen difference at rest and during exercise in ten patients with aortic regurgitation. Conventions as in Fig. 2.

patients the rise in the cardiac output was less than would be expected (F.B., O.W., P.W., and G.W.). Consequently, as noted in Fig. 1, the slopes of the lines connecting the resting and exercise $\frac{\text{oxygen consumption}}{\text{cardiac index}}$ ratio are steeper in these patients than in the normal patient represented by the enclosed area (Fig. 7).

When the blood flow was inadequate to meet the oxygen demands of the tissues, the extraction of oxygen was increased (F.B., A.M., J.R., and G.W.). This widened arteriovenous oxygen difference was more pronounced during exercise than during rest (Fig. 8).

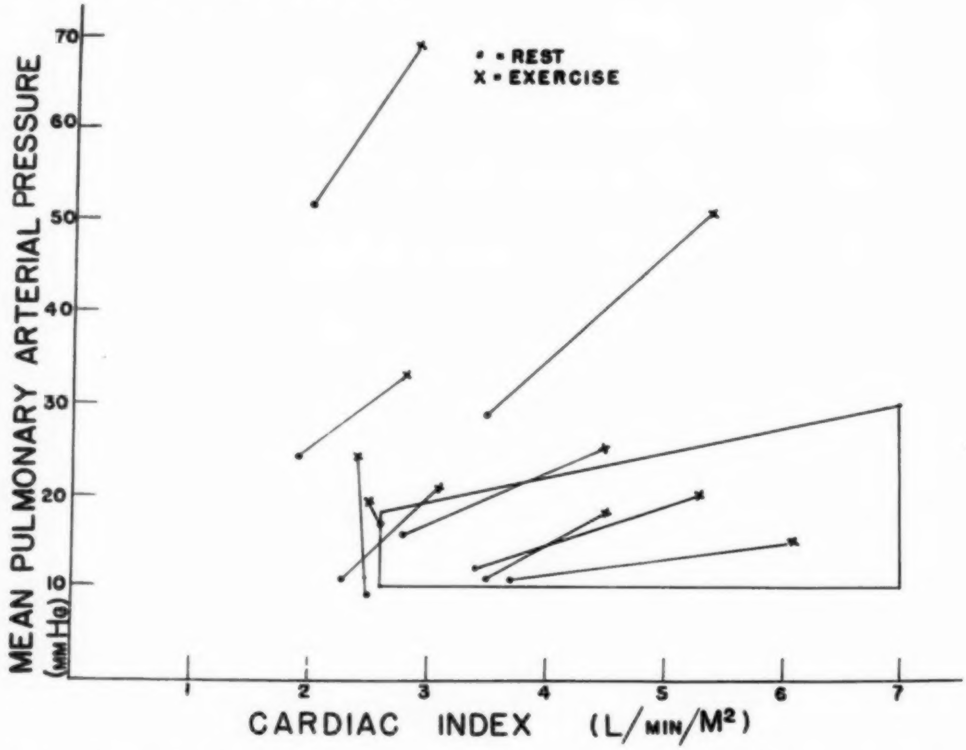


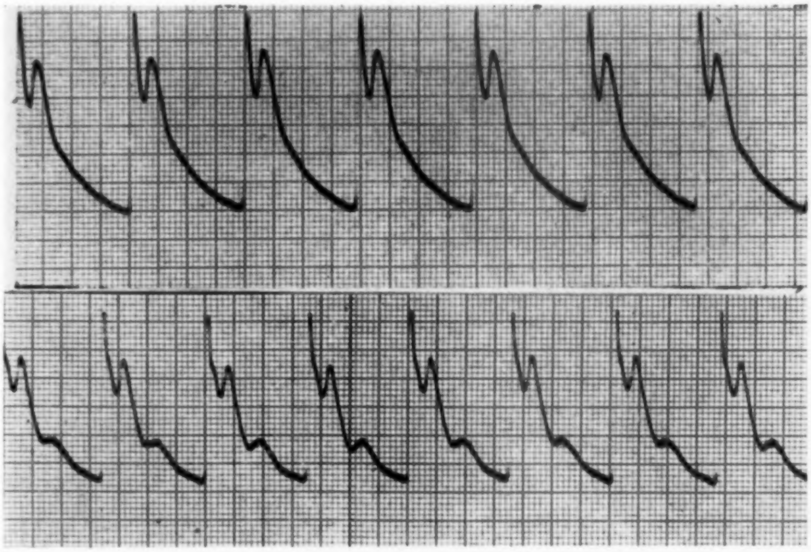
Fig. 9.—The relationship of the mean pulmonary artery pressure and the cardiac index at rest and during exercise in ten patients with aortic regurgitation. Conventions as in Fig. 3.

The mean pulmonary arterial pressures at rest were normal in nine patients and elevated in four. "Pulmonary venous capillary" pressure was elevated in three of the latter group. In the fourth patient (S.B.) the "capillary" pressure was normal, and the pulmonary arterial pressure was only slightly above normal. In one patient (G.W.) with "pulmonary venous capillary" and pulmonary arterial hypertension, mitral regurgitation to a minimal degree was found; and in a second (P.W.), mitral regurgitation was suspected.

The effect of exercise upon the pulmonary arterial circulation was obtained in ten patients (Fig. 9). In seven of these patients the resting mean pulmonary arterial pressure was normal and remained so in three during exercise. Pulmonary

hypertension developed in four. In the remaining three patients, the resting pulmonary arterial pressure was elevated and rose still higher during exercise. In two (P.W. and G.W.) with resting pulmonary hypertension, mitral regurgitation was found in one and suspected in the other (P.W.). The "pulmonary venous capillary" pressure curve in one case demonstrated a tall V wave which is frequently observed in mitral regurgitation.[23] The pulmonary arteriolar resistance was calculated in ten cases. It was within normal limits in five, slightly elevated in four, and moderately elevated in one (G.W.).

The work of the right ventricle was within normal limits for all but one patient (P.W.). There was evidence of right ventricular failure in one patient (H.M.), in whom the end-diastolic pressure in the right ventricle was 10 mm. Hg. The "pulmonary venous capillary" pressure was elevated as well. The mitral valve was normal in this patient.


A.

B.

Fig. 10.—Brachial arterial pressure curves obtained from patients with aortic regurgitation. *A*, Patient S.L.; *B*, Patient P.W.

The brachial arterial pressure curves were obtained in all but one patient. The pulse pressure ranged between 66 and 150 mm. Hg, averaging 103. The upstroke was steep. The peak of systole was reached either early or in normal time in eight cases (Fig. 10). In four instances the peak of systole was delayed, yet occurred earlier than was found in those patients with "pure" aortic stenosis. In each of these there was an anacrotic notch or slurring of the upstroke, which was observed in predominant aortic stenosis. In one of these, aortic stenosis was felt to be of moderate degree. However, in all, regurgitation was the predominant lesion.

The dicrotic incisura was flattened or absent in all but two cases. In these the dicrotic wave occupied a position lower than normal on the catacrotic limb. Frequently, several peaks are observed.

The Valsalva maneuver was performed in three patients in this group. In no instance was an overshoot in the blood pressure obtained in the poststraining

TABLE IIB. PHYSIOLOGIC DATA: AORTIC REGURGITATION PREDOMINANT LESION

CASES	O_2 CONS. C.C./MIN./M^2		A-V O_2 DIFF. VOL. (%)		CARDIAC OUTPUT L./MIN.		CARDIAC INDEX		PULSE RATE		STROKE INDEX		PULMONIC CIRCULATION: PA PRESS. (MEAN) MM. HG		PULMONIC CIRCULATION: RV PRESS. S/D MM. HG	PULMONIC CIRCULATION: RA PRESS. MM. HG	PULMONIC CIRCULATION: PVC PRESS. MM. HG	PULMONIC CIRCULATION: PA RESIS. DYNES SEC. CM.$^{-5}$	PULMONIC CIRCULATION: RV WORK KG./MIN./M^2	SYSTEMIC CIRCULATION: PRESS. S/D MM. HG	SYSTEMIC CIRCULATION: PULSE PRESS.	SYSTEMIC CIRCULATION: PEAK OF SYS-TOLE SEC.	BA O_2 SAT. (%)	
	R	E	R	E	R	E	R	E	R	E	R	E	R	E									R	E
T.V.	128	298	4.5	6.6	5.7	9.2	2.8	4.5	75	91	37	49	(16)	(25)	35/3	(−2)	(10)	82	0.72	190/40	150	0.09	92	91
R.B.	147.2	382	4.4	7.2	6.2	9.8	3.4	5.3	81	99	42	54	(12)	(19)	26/6	0	(7)	65	0.59	167/48	119	0.03	92	94
F.B.	130	267	5.7	8.5	4.1	5.7	2.6	3.1	72	96	32	32	(11)	(21)	22-26/9-15	0	—	—	0.41	132/34	98	—	92	91
S.B.	145	228	—	—	—	—	—	—	81	—	—	—	(21)	—	—	—	(11)	—	—	125/23	102	0.07	—	—
A.M.	137	234	5.4	9.8	4.4	4.1	2.5	2.4	86	105	29	23	(16)	(24)	20-24/0	(2)	(10)	120	0.50	108/42	66	0.18	96	93
H.M.	95.5	210	5.1	7.3	3.1	4.7	1.9	2.8	73	82	26	34	(24)	(33)	30/10	(2)	(18)	155	0.57	150/61	90	0.19	95	90

M.R.	—	—	—	—	—	—	—	—	—	—	—	—	** 30-34 / 10-19	—	43 / 0-12	(10)	(6)	—	—	—	—	—	—	—
J.R.	147	280	5.8	11.3	5.0	4.8	2.6	2.5	72	82	36	31	(17)	(19)	20-28 / 0-3	(4)	(10)	112	0.48	181 / 71	110	0.16	92	94
E.McC.	122	—	4.9	—	3.9	—	2.7	—	80	—	34	—	—	—	—	—	—	—	—	144 / 60	84	0.20	90	—
W.O.	150	314	4.3	7.0	5.8	7.4	3.5	4.5	98	125	36	36	(11)	(8)	—	—	(4)	97	—	130 / 40	90	0.11	93	92
S.C.	114	—	3.9	—	5.0	—	2.9	—	7[illegible]	—	41	—	(11)	(—)	19 / 3	(3)	(6)	80	0.33	152 / 40	112	0.04	91	—
P.W.	162	418	4.6	7.7	5.6	8.7	3.5	5.4	90	132	39	41	(29)	(51)	—	(2)	(18)	157	1.36	119 / 37	82	0.09	87	93
S.L.	114	399	3.1	6.5	6.4	10.7	3.7	6.1	87	115	43	53	(11)	(15)	19-22 / 2-4	(2)	(8)	38	0.48	195 / 46	149	0.03	92	90
G.W.	150	294	7.1	8.8	3.6	5.8	2.1	2.9	80	100	26	[illegible]9	(52)	(69)	—	—	(30)	490	—	128 / 44	84	0.17	93	81

**Systolic/Diastolic

period.* During the straining period there was a marked change in the pulse pressure and the contour of the curve. The former became much smaller and the numerous peaks observed in the control pressure tracing were replaced by a smooth curve with but one peak. The dicrotic notch was low, approaching the end-diastolic pressure. There was no appreciable change in the contour of the curve in the poststraining period. This is undoubtedly due to the fact that no overshoot in the blood pressure occurred in this period.

DISCUSSION

Disease of the aortic valve resulting either in obstruction or in regurgitation places the chief burden upon the left ventricle. Although the dynamics of the latter may differ in these conditions, this chamber is the one immediately affected.

It has been demonstrated experimentally[34] that the intraventricular pressure exceeds the aortic pressure when the aortic lumen is reduced in size. Similarly, we have observed that in patients with aortic stenosis at the time surgery was being performed upon the aortic valve, the pressure in the left ventricle is higher than that in the aorta. It is undoubtedly this pressure gradient across the narrowed valvular area which maintains the output of the left ventricle. Accordingly, we have found the cardiac output to be normal or elevated in the majority of patients, with predominant aortic stenosis. Eight patients, however, in our series showed a low cardiac output in the presence of a normal oxygen consumption. Although the cardiac output rose during exercise, it was inadequate to meet the oxygen demands of the tissues in more than one-half of the patients in which this determination was made. The inability to maintain or adequately increase the cardiac output during exercise seemed due to several factors:

1. The possibility of left ventricular failure deserves first consideration. Since the end-diastolic pressure in the left ventricle in these patients was not measured, this factor cannot be eliminated completely. Hickam and Cargill[35] showed that patients in left ventricular failure may show little or no increase in the cardiac output during exercise. In this regard it is of interest that in three patients without coexisting mitral valvular disease the resting "pulmonary venous capillary" pressure was elevated. Since this measurement is an index of the left atrial pressure,[36] it is most probable that the "pulmonary venous capillary" hypertension in these individuals is due to left ventricular failure.

2. A second cause for limiting the cardiac output either at rest or during exercise is the presence of mitral stenosis[21] or mitral regurgitation.[23] Three of the eleven patients (E.C., M.C., and D.R.) with a low-resting cardiac output had predominant mitral stenosis. All but one of the patients with coexisting mitral valvular disease, six in all, showed an inadequate rise in the cardiac output during exercise.

3. Right ventricular failure as a cause for limitation of the cardiac output probably plays a minor role in this group of individuals. Evidence of right

*Recently we have studied cases with predominant aortic regurgitation in whom an overshoot in the blood pressure was observed during the poststraining period.

ventricular failure at rest was present in only one patient among those with predominant aortic stenosis, and this patient had a moderately severe coexisting mitral stenosis. Right ventricular failure as a factor during exercise cannot be entirely eliminated, since the pressure in the right ventricle was not obtained at that time. Miller and associates[21] have shown that right ventricular failure may develop during exercise in patients with mitral stenosis. It is entirely possible that right ventricular failure may be an additional factor in those individuals with or without mitral valvular disease in whom pulmonary hypertension is present.

4. The presence of mitral regurgitation may play a role in some cases. In two patients (E.C. and F.K.) in Group A a significant degree of mitral regurgitation was present. In one, the cardiac output was low. With the more rapid cardiac rate which occurs during exercise, a larger percentage of time of the cardiac cycle is spent in systole. Hence, a relatively greater amount of blood will be lost through the incompetent mitral valve, thus limiting the effective cardiac output.

5. Finally, the obstruction at the aortic orifice, per se, may be a limiting factor. It has been shown in animals[34] that when the stenosis experimentally produced in the aorta is sufficiently severe, the aortic blood flow is reduced. With increasing degrees of narrowing of an orifice, the pressure gradient across this orifice must increase to maintain the flow. When the ventricle is unable to increase the pressure sufficiently, the output falls.

In summary, then, the failure either to maintain or increase the cardiac output to meet the demands of the tissues in patients with predominant aortic stenosis may be due to: (1) the coexisting presence of mitral valvular disease, either stenosis or regurgitation; (2) left ventricular failure; or (3) the presence of the obstruction at the aortic valve, per se. Right ventricular failure is an infrequent cause.

It has been observed in patients with predominant mitral stenosis that when the cardiac output was inadequate to meet the oxygen demands of the tissues, extraction of oxygen by the tissues was increased. Although this is occasionally observed during rest, it is more frequently found during exercise. As pointed out previously,[21] the widening of the arteriovenous oxygen difference may serve as a guide to the patient's ability to maintain or to increase his cardiac output. In general, the arteriovenous oxygen difference varies inversely with the cardiac output. That is, the less adequate the cardiac output, the greater the arteriovenous oxygen difference. Conversely, the more the heart is able to meet the tissue demands, the smaller the arteriovenous difference.

The pulmonary circulation is frequently normal in predominant aortic stenosis. Consequently, the pulmonary arterial pressure was normal in twelve patients with "pure" aortic stenosis. Of those individuals, fourteen in number, who had pulmonary hypertension, the latter could be attributed directly or indirectly to the presence of mitral stenosis in five. Two of these five patients showed elevated "pulmonary venous capillary" pressures. The pulmonary hypertension in the remaining three, then, was probably due to pulmonary vascular changes. In several patients the pulmonary hypertension can be

attributed to left ventricular failure. This is based upon the findings of an elevated "pulmonary venous capillary" pressure in each case, in the absence of mitral valvular disease. There were at least five patients with pulmonary hypertension and with no evidence of either left ventricular failure or of mitral valvular involvement. The elevated pulmonary arterial pressure in these patients is due to increased pulmonary vascular resistance. The latter probably results from pulmonary vascular changes, the nature of which is not clear. These changes may be either functional or organic, or both. It is possible that they are similar to those observed in patients with mitral valvular disease described by Weiss and Parker[37] and Edwards and associates.[38] Repeated attacks of left ventricular failure may provide the stimulus for their production. It is entirely possible that the right ventricular failure which is occasionally observed in individuals with predominant aortic stenosis may be in part, at least, due to the presence of these arteriolar changes. In the majority of instances, right ventricular failure in these patients follows upon left ventricular failure. Occasionally, however, failure of the right side of the heart is observed in the absence of any evidence of failure of the left side of the heart. Some observers have attributed this to the presence of the so-called Bernheim syndrome. This is probably an infrequent cause. It is suggested that pulmonary vascular disease in patients with aortic stenosis is present more frequently than is generally believed and that these changes in the pulmonary vascular bed by virtue of an increase in the pulmonary vascular resistance place a load upon the right ventricle. This increased amount of work, plus any myocardial disease which may be present, may be sufficient to produce right ventricular failure in the absence of left ventricular failure.

The peripheral blood pressure is usually normal in patients with aortic stenosis. The pulse pressure is within the normal range in the majority of the cases. This is undoubtedly due to the prolongation of systolic ejection. Consequently, the peak of systole is constantly delayed (Table IIA). The brachial arterial pressure curve is characteristic in patients with predominant aortic stenosis. Unlike the series reported by Feil and Gilder[39] the anacrotic phenomenon (i.e., either a true anacrotic notch or a mere interruption or "slur" of the upstroke of the brachial arterial pressure curve) appeared more frequently in our cases than the double-summit variety observed by them. This is probably due to the fact that the present series (Group A) contains patients with predominant aortic stenosis, regurgitation being either minimal or absent in the majority of the cases. Katz and associates[34] showed that an anacrotic notch followed by multiple vibrations is observed in the central aortic pressure curve obtained in experimentally produced aortic stenosis. They pointed out that the notch is probably due to the sudden fall in the lateral pressure in the aorta beyond the stenosis resulting from the increased velocity of flow past the constricted lumen.

Feil and Katz[43] found that the anacrotic notch was present in the radial pulse in patients with aortic stenosis and felt that it was a peripheral manifestation of the sudden break occurring in the central pulse. Dow[40] claims that the violence of systolic discharge is so reduced by the stenosis that the standing waves are not set up, and hence the peripheral pulse reproduces the central pulse form. The peripheral pulse curve is practically always free of the vibrations

beyond the anacrotic notch. In only one case (W.E.) did the peripheral pulse demonstrate multiple vibrations on the anacrotic limb. In this individual, a patient with congenital aortic stenosis and with the smallest pulse pressure observed in this series, a central aortic curve was recorded through a catheter passed into the aorta from the brachial artery. The aortic curve was similar to the peripheral one. Perhaps in this individual the force of ejection was sufficiently reduced to allow for almost exact reduplication of the central pulse peripherally.

Marked changes have been observed in the brachial arterial pressure curve during the Valsalva maneuver in these patients with aortic stenosis. An overshooting of the blood pressure is frequently observed in the poststraining period. Unlike mitral stenosis[41] there is in aortic stenosis a strong muscular organ, the left ventricle, just proximal to the obstruction. The left ventricle, then, in the majority of instances is capable by its compensatory mechanisms, dilatation and hypertrophy, of ejecting the blood received by it in the poststraining period, thus producing an overshoot in the blood pressure. The latter then, reflexively through the carotid and aortic sinuses, is responsible for the bradycardia observed during this time.

More striking than the slowing of the pulse is the pronounced change observed in the contour of the curve. During the straining period, when the venous return is markedly reduced as a result of the increased intrathoracic pressure, the anacrotic or double-summit pulse observed in the control tracing may be replaced by a small smooth pulse with a single peak, resembling a normal curve. After the release of the strain as the venous return is increased above normal, the double-summit or anacrotic characteristics gradually return. If an overshoot in the blood pressure is obtained during this period, a double-summit pulse may be converted into the anacrotic pulse, or a pre-existing anacrotic notch may assume a lower position than it did in the control tracing. Thus it appears that as the stroke volume and pulse pressure become smaller, the anacrotic notch climbs up the anacrotic limb until it gradually disappears. Conversely, when the stroke volume exceeds the control levels in the poststraining period, the anacrotic notch or double summit gradually reappears and the notch descends on the anacrotic limb. Hence, although it may be true that the severity of the stenosis determines the position of the notch on the anacrotic limb,[34] it appears that the stroke volume or pulse pressure is a factor as well. We have observed individuals (W.C. and J.B.) in whom the double-summit variety brachial pressure curve was found and who had severe degrees of aortic stenosis. It is of interest that these patients had very small pulse pressures (Table IIA). Further evidence that the pulse pressure plays a role in determining the contour of the peripheral pressure curve in aortic stenosis is found in an examination of the tracings taken in individuals with auricular fibrillation (Fig. 5). In the latter the pulse pressure varies from beat to beat, depending upon the diastolic filling time. After a short interval when the diastolic filling time is markedly reduced, a small complex is obtained which appears normal (fourth beat in Fig. 5). However, following a longer interval (fifth beat in Fig. 5) when the diastolic filling time is long, allowing for more complete filling of the left ventricle, the stroke volume is greater, and a large complex now characteristic of aortic stenosis is obtained.

The Valsalva maneuver has been of aid in explaining certain findings in the brachial arterial pressure curve. Occasionally one finds a small notch on the catacrotic limb between the peak of systole and the dicrotic incisura (Fig. 4,*B*). It is difficult to be certain whether this is a true abnormality or merely an artifact. If in the poststraining period an overshoot in the blood pressure is obtained and this notch can be made to move to a position on the upstroke of the brachial artery curve, it represents an abnormality. This was obtained in one patient (M.C.) in this series, and since has been found in others. If, however, this does not occur, it probably represents an artifact due to afterfling of the writing pen. In order to rule out such an abnormality, an overshoot in the blood pressure must be obtained in the poststraining period.

Finally, it is suggested that recording of the brachial arterial pressure curve during and immediately following the Valsalva maneuver may be of aid in detecting mild degrees of aortic stenosis in patients with apparently normal brachial arterial pressure curves. The importance of detecting aortic stenosis in patients undergoing mitral commissurotomy is evident. Stenosis of the aortic valve considered to be mild clinically may become of great dynamic significance immediately following mitral commissurotomy. As a result of the operation, the filling of the left ventricle is suddenly increased. The poststraining period of the Valsalva maneuver is thus simulated. The stenosis at the aortic orifice under these acute conditions assumes a greater physiologic significance. The obstruction now becomes relatively more severe. The left ventricle may or may not be able to discharge effectively the sudden increase in the amount of blood it now receives. Mitral commissurotomy has resulted in death shortly after surgery in individuals in whom autopsy examination has revealed moderate to severe aortic stenosis which was clinically unappreciated preoperatively. A brachial arterial pressure curve is extremely valuable in such cases. If the resting brachial arterial curve is unrevealing, the Valsalva maneuver as described above may be decisive. It is now a general practice in our laboratory in evaluation of candidates for mitral valve surgery to record the brachial arterial pressure curve at rest, during, and immediately following the Valsalva maneuver. It is a simple test to perform, the recording being made through an indwelling needle in the brachial artery.

The hemodynamic alterations upon the circulation resulting from aortic regurgitation are in some respects similar to those of aortic stenosis. Although a mild degree of aortic stenosis is frequently present in rheumatic aortic regurgitation, basically there is insufficiency of the valve with regurgitation of blood into the ventricle. The diastolic length of the ventricle thus is increased when the inflow through the mitral valve is maintained, with subsequent more forceful contraction of the ventricle according to Starling's law. The systolic discharge is thus greater than normal. Wiggers and Maltby[42] demonstrated that the magnitude of backflow varies with the size of the leak and can be 50 per cent or more when the cusps are rendered totally deficient. No attempt was made in the present study to quantitate the regurgitant flow.

There was a wide range in the resting cardiac index in patients with aortic regurgitation, the average being within the normal range. Several patients had resting cardiac indices below normal. The presence of mitral regurgitation may

have accounted for the low output in one (G.W.). The presence of the deformity itself at the aortic valve may be responsible in at least two, i.e., the total systolic discharge of the ventricle was not sufficient to maintain a normal cardiac output. The pulmonary arterial pressures in these patients (F.B. and O.W.) remained within normal limits during exercise. Left ventricular failure then, as a factor in limiting the cardiac index in these individuals, is open to question. The inadequate rise in cardiac output during exercise may, in other instances, however, be due to left ventricular failure. Hence, the same factors tend to limit the cardiac output in patients with aortic regurgitation as in aortic stenosis. Similarly, when the cardiac output is insufficient to meet the demands of the tissues, the extraction of oxygen by the tissues is increased.

Pulmonary arterial pressure is generally within normal limits in aortic regurgitation. The most frequent cause of pulmonary hypertension is left ventricular failure. In one patient (G.W.) with only minimal mitral regurgitation but with rather severe pulmonary hypertension in the pulmonary bed, pulmonary vascular disease was suspected. This individual was the only patient in this group (B) with markedly elevated pulmonary vascular resistance.

Our observations on the brachial arterial pressure curve in patients with aortic regurgitation are similar to those of Feil and Gilder.[39] The rise in ejection is steep, and the peak of systole occurs early. Several peaks are frequently observed. The descent is rapid to the point where the dicrotic incisura is expected. The most constant abnormality is flattening or disappearance of the dicrotic incisura and wave. According to Alexander[44] this is due to the elimination of the standing wave primarily because of the regurgitation at the aortic orifice. When a dicrotic incisura is present, it occupies a lower position on the catacrotic limb than normally. In the majority of cases a true anacrotic notch is not seen unless the element of stenosis becomes great. Even in these cases the peak of systole is not delayed to the degree that is observed in cases of predominant aortic stenosis.

The response to the Valsalva maneuver in patients with predominant regurgitation at the aortic valve differs from those with stenosis. In the three patients observed in this group no overshoot in the blood pressure was obtained in the poststraining period. Consequently, there was no change in the pulse contour. This was in agreement with Hamilton and associates.[45] Although this may be true in the majority of the cases, it may not be so in all. Recently, we have observed cases of aortic regurgitation in which an overshoot in the blood pressure was found in the poststraining period.[46] We do not believe that the response to the Valsalva maneuver can differentiate a predominant aortic stenosis from a predominant aortic regurgitation. The resting pulse contour, however, is of great aid in this regard.

CORRELATION OF CLINICAL AND PHYSIOLOGIC FINDINGS IN PATIENTS WITH AORTIC VALVULAR DISEASE

The most common symptom of patients with aortic valvular disease is dyspnea, particularly during activity. This is probably related to pulmonary

congestion. During the mild form of exercise performed in this study, pulmonary hypertension developed in many patients. It is reasonable to assume that, with more strenuous activity, this would occur in a larger number. Although in some patients the pulmonary congestion is due to coexisting mitral stenosis, in those with "pure" aortic stenosis and regurgitation, left ventricular failure probably plays an important role. The paroxysmal nocturnal dyspnea so often observed is a manifestation of a failing left ventricle.

Fatigue was a common symptom in our patients. This was particularly prominent during activity. It may be related to the inadequate cardiac output frequently observed during exercise.

Syncope, dizziness, and vertigo are also frequently observed in aortic valvular disease, more so in stenosis, however, than in regurgitation. The pathogenesis of these symptoms is not clear. In those individuals giving a history of dizziness or syncope, although the resting cardiac output was normal in many, all but one had an inadequate rise in cardiac output during exercise. However, a larger number of patients demonstrating an inadequate rise in the cardiac output during exercise gave no history of these symptoms. A hyperactive carotid sinus has been suggested.[47] We recently observed this in a patient with aortic stenosis in whom during cardiac catheterization there was occasion to put pressure upon the neck. Immediately thereafter the patient complained of dizziness and weakness, and her skin became pale, cold, and clammy. Examination of the electrocardiogram at this time revealed the sudden appearance of a marked sinus bradycardia. This was followed by a nodal rhythm. Since a hyperactive carotid sinus was suspected, atropine was immediately administered. Shortly thereafter the rhythm returned to normal, via a short run of auriculoventricular dissociation. In this individual the cerebral symptoms may be on the basis of hyperactive carotid sinus.

Perhaps the most distressing symptom in aortic valvular disease is chest pain. It was present in 50 per cent of our patients with aortic stenosis, and 60 per cent of those with aortic regurgitation. Many explanations have been given for the pathogenesis of this symptom in aortic stenosis. Some authors believe it is related to concomitant atherosclerosis of the coronary artery.[47] Angina, however, occurs in the presence of normal coronary arteries. Contratto and Levine[48] attribute it to the relative myocardial ischemia secondary to increased velocity of flow past the coronary ostia, producing a suction effect. Green and Gregg[49] found a decreased minute flow through the coronary arteries in experimental aortic stenosis. The flow to the myocardium during systole is markedly reduced due to the increased resistance to flow in the coronary bed, resulting from the high intraventricular pressure during this phase. Hence, the total coronary flow is decreased. Even if the coronary flow were normal in human aortic stenosis, a relative coronary insufficiency would be present. Coronary insufficiency results from an imbalance between two factors: the need for coronary flow and actual coronary flow. In aortic stenosis, because of the markedly increased work of the left ventricle, the need for coronary flow is proportionately increased. Since the actual flow is either normal or reduced, coronary insufficiency results. We have observed rather prompt relief of angina in patients with aortic stenosis following aortic commissurotomy.[50] This would favor the theory that the chest pain is due

to relative coronary insufficiency in these cases rather than to organic coronary artery disease.

Green[51] showed in experimental animals and Bing and associates[52] demonstrated by cardiac catheterization that the coronary flow is actually increased in aortic regurgitation. Since this flow is apparently insufficient to meet the myocardial demands, particularly during activity, coronary insufficiency is present, resulting in angina.

Our studies indicate that the most valuable single study in aortic valvular disease is the peripheral arterial pressure curve. Frequently, the clinical findings are inconclusive. Although a systolic murmur was heard in all cases of aortic stenosis, the presence of a systolic thrill was absent in at least five. It appears, then, that the thrill is not necessary for the diagnosis of aortic stenosis. The second aortic sound was either markedly diminished or absent in the majority of cases. Occasionally it is normal or even increased in intensity. The peripheral pulse may not be characteristic by palpation.

An aortic diastolic murmur transmitted and heard best at the left sternal border (usually at the third intercostal space) is a constant feature in aortic regurgitation. An aortic diastolic murmur is also frequently heard in individuals with predominant aortic stenosis. Although the diastolic pressure is generally lower and the pulse pressure is wider, the pulse is not always typically water hammer in regurgitation. Interpretation of the pulse by palpation is often difficult. Under such circumstances the peripheral arterial pressure curve is extremely valuable. The contour is characteristic. On occasion, however, particularly in mild degrees of aortic stenosis, the typical picture may not be seen. Our studies suggest that phasic recording of the brachial arterial pressure through an indwelling needle during and immediately following the Valsalva maneuver may be decisive in establishing the diagnosis.

SUMMARY

1. The circulatory dynamics in forty patients with aortic valvular disease was studied by catheterization of the right side of the heart and peripheral arterial pressure curves. Twenty-six patients had predominant aortic stenosis; fourteen, predominant aortic regurgitation.

2. Measurements were made at rest and during exercise. The response to the Valsalva maneuver was determined.

3. Although basically obstruction and regurgitation at the aortic orifice differ, the circulatory patterns were in many respects similar.

4. The resting cardiac output is generally within normal limits. Although a rise in the cardiac output is the rule during exercise, it is frequently less than would be expected. The limited cardiac output either at rest or during activity may be due to: (a) the presence of coexisting mitral disease; (b) left ventricular failure; and (c) the lesion (stenosis or regurgitation) per se.

5. The pulmonary circulation is usually normal. Pulmonary hypertension, when present, may be due to several factors: (a) left ventricular failure; (b) coexisting mitral stenosis; or (c) pulmonary vascular changes. Pulmonary vascular changes may be important contributing factors in the production of right ventricular failure in some cases.

6. The peripheral arterial pressure curves are characteristic in aortic stenosis and aortic regurgitation.

7. Marked changes are noted in the brachial arterial pressure tracings during and immediately following the Valsalva maneuver. It is suggested that this maneuver may be helpful in bringing out the anacrotic phenomenon and elucidating certain findings in the resting peripheral pressure curve.

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THE BALLISTOCARDIOGRAM IN AORTIC STENOSIS

B. van Lingen, M.D. (Rand), J. H. Gear, M.R.C.P. (Lond.), Joanna Whidborne, B.Sc. (Lond.), and Margaret L. Lister, B.Sc. (Hon.)

Johannesburg, South Africa

PREVIOUS studies have demonstrated a relatively specific ballistocardiogram in patients with coarctation of the aorta[1-3] or with thrombosis of the bifurcation of the aorta.[4] This pattern is characterized by an absent or small and distorted K wave. The purpose of the present paper is to analyze the ballistocardiographic findings in subjects with aortic stenosis or with a combined aortic stenosis with incompetence and to describe a pattern characteristic of aortic stenosis.

MATERIAL AND METHODS

Seventeen patients were investigated; aortic valvular stenosis was considered to be present in three cases. The diagnosis was based on the presence of a systolic murmur at the base of the heart together with a typical diamond-shaped systolic murmur on phonocardiography. An associated aortic incompetence was diagnosed in fourteen cases being characterized by a decrescendo diastolic murmur continuous with the second heart sound which was heard best down the left sternal border. Additional evidence consistent with aortic valvular disease was present in some cases. Such evidence included a systolic thrill at the base of the heart and over the carotid arteries, an absent or diminished second heart sound, a peripheral pulse considered to be plateau, bisferiens, or collapsing in type, and electrocardiographic and radiologic evidence of left ventricular enlargement. All cases were considered to have rheumatic heart disease and the incidence of associated valvular lesions has been tabulated (Table I).

Five cases of syphilitic aortic incompetence were also studied. These cases gave no history of rheumatic fever and clinical evidence of aortic stenosis was not present. A strongly positive blood Wassermann reaction was found in four of these patients. They differed from the cases of aortic stenosis with or without incompetence in that all had been or were actually in congestive cardiac failure at the time of examination.

The ballistocardiograms of twenty-eight normal subjects and 200 patients with heart disease without involvement of the aortic valve were examined. The tracings of the normal subjects were studied in a manner similar to that used in the cases of aortic stenosis or combined aortic stenosis and incompetence while

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From the Department of Medicine, Witwatersrand University, Johannesburg, the Cardiac Clinic, Johannesburg General Hospital, and the Council for Scientific and Industrial Research, South Africa.

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Table I

	NORMAL	AORTIC INCOMPETENCE	AORTIC STENOSIS WITH OR WITHOUT INCOMPETENCE				
			TOTAL	J-K ANGLE 7° OR LESS	J-K ANGLE 8° OR MORE	WITH MITRAL STENOSIS	WITHOUT MITRAL STENOSIS
Number	28	5	17	6	11	9	8
Average age, years	26	52	31	32	28	34	29
Average J-K angle, degrees	1	2	12	5	17	14	10
Range J-K angle, degrees	0 to 7	0 to 5	2 to 34	2 to 7	8 to 34	2 to 34	2 to 17
Average stroke force, Gm.	43	31	26	50	21	32	31
Average heart rate, per min.	57	85	77	88	72	70	86
Average minute force, Gm.	2,447	2,600	2,455	4,154	1,530	2,080	2,880
Average blood pressure, mm.Hg	115/75	128/43	125/77	135/68	119/82	126/75	124/79
Average pulse pressure	40	85	48	67	37	51	45
Pulse normal	28	0	3	0	3	1	2
Plateau	0	0	5	2	3	2	3
Bisferiens	0	0	3	0	3	3	0
Collapsing	0	5	6	4	2	3	3
High-frequency ballistocardiogram*	0	0	10	2	8	6	4

*This refers to a ballistocardiogram with a small and often distorted K wave and a deep M wave referred to in the text.

the pattern of the ballistocardiogram was the only feature studied in the 200 patients with heart disease.

Low-frequency critically dampened ballistocardiograms were recorded on a table similar in design to that described by Nickerson and Curtis.[5] High-frequency records were obtained from a ballistocardiograph similar in principle to

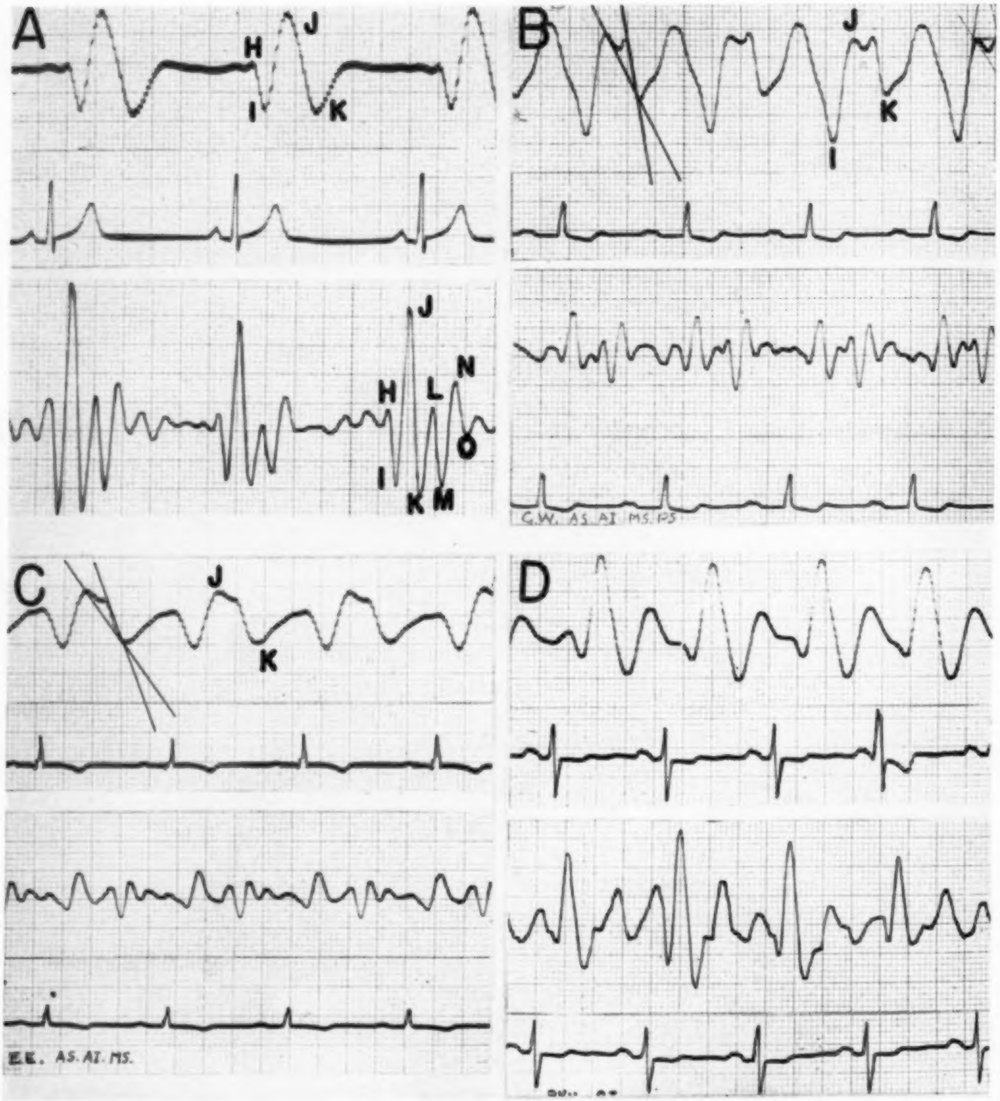

Fig. 1.—The upper tracing of each figure (*A*, *B*, *C*, *D*) shows a low-frequency critically damped ballistocardiogram. Simultaneously recorded electrocardiograms are shown below the ballistocardiograms. *A* illustrates the ballistocardiogram of a normal subject; *B* and *C*, those of two patients with aortic stenosis and incompetence; *D*, that of a patient with pure aortic incompetence. The arbitrary method of measuring the angulation of the J-K segment of the low-frequency critically damped ballistocardiogram is shown in the first complex of *B* and *C*. The details of this procedure are discussed in the text.

that used by Starr and associates.[6] Tracings were taken with respiration suspended in mid-inspiration, in deep inspiration and in deep expiration. In the case of high-frequency ballistocardiograms, records were also taken while the subject was breathing normally. An electrocardiogram recorded simultaneously served as a reference tracing.

A measure of the systolic force of low-frequency ballistocardiogram was obtained by converting the I-J amplitude measured in millimeters into grams.[7] This was achieved by relating the I-J amplitude to the displacement produced by a known weight.[5] The minute systolic force[7] was estimated as the product of the systolic force and the heart rate. Time intervals were measured between the beginning of the Q or R wave of the electrocardiogram and the H, I, J, and K waves of the ballistocardiogram.[7]

An empirical method was used to measure the degree of angulation or outward bowing of the J-K segment of the low-frequency ballistocardiogram (Fig. 1, *B*). Two lines were drawn from the apex of the K wave. One was drawn to the apex of the J wave and the other to the outwardly bowed or angulated portion of the J-K segment, the angle between these two lines being a measure of the degree of angulation or bowing. It was necessary to standardize the paper speed and the displacement produced by the calibration weight as both these factors could alter the degree of angulation. The paper speed was constant in all records and was similar to that of the conventional electrocardiograph. An arbitrary convention was adopted in regard to the calibration and a weight of 15 grams was required to displace the tracing 10 mm. When necessary the ballistocardiogram was reconstructed to conform with this convention.

RESULTS

The low-frequency critically damped ballistocardiogram in cases of aortic stenosis with or without incompetence showed a characteristic outward bowing or angulation of the J-K segment (Table I, Fig. 1, *B*,*C*). The angle drawn to represent this bowing exceeded 7 degrees in eleven of these seventeen cases, whereas it was seven degrees or less in a group of twenty-eight normal subjects (Fig.1, *A*), and in 200 patients with other types of heart disease including five cases with syphilitic aortic incompetence (Fig. 1, *D*.).

A comparison of these cases of aortic stenosis or aortic stenosis and incompetence with a J-K angle of 7 degrees or less (average 5 degrees) with those with larger angles (average 17 degrees) showed several interesting findings. The group with large J-K angles had on an average a lower systolic force, a lower minute systolic force and a smaller pulse pressure than the group with a small J-K angle (Table I). The presence or absence of mitral stenosis in association with an aortic valvular lesion did not appear to alter the ballistocardiographic findings (Table I). A comparison between the cases with aortic stenosis and those with both aortic stenosis and incompetence was not considered to be worthwhile because of the small number of cases of pure aortic stenosis examined.

The time intervals between the electrocardiogram and the deflections of the low-frequency ballistocardiogram were often similar in the various types of heart disease examined. The average of these measurements in the various types of

Table II. Mean Values and Range for Various Time Intervals Between the Electrocardiogram and Low-frequency Critically Damped Ballistocardiogram

	NO.	Q-H	Q-I	Q-J	Q-K	H-I	I-J	J-K	H-J	H-K
					SECOND					
					Normal Subjects					
Average	28	0.133	0.218	0.360	0.570	0.084	0.140	0.209	0.220	0.437
Range		0–0.18	0.16–0.27	0.30–0.42	0.48–0.64	0–0.08	0.11–0.18	0.14–0.24	—	—
					Aortic Stenosis and Aortic Stenosis and Incompetence					
Average	17	0.105	0.194	0.359	0.568	0.098	0.159	0.207	0.257	0.464
Range		0–0.16	0–0.25	0.28–0.44	0.48–0.67	0–0.16	0.12–0.20	0.12–0.29	—	—
					Aortic Incompetence					
Average	5	0.145	0.230	0.365	0.537	0.089	0.133	0.173	0.222	0.395
Range		0–0.18	0.20–0.27	0.30–0.43	0.46–0.60	0.06–0.10	0.10–0.14	0.13–0.18	—	—

heart disease, however, showed deviations from the normal which will be considered later (Table II).

The pattern of angulation of the J-K segment of the Nickerson ballistocardiogram was often accentuated in the cases of aortic stenosis with or without incompetence when the respiration was suspended in deep inspiration, but was only found in one of these cases when the respiration was suspended in deep expiration. Among the normal subjects and patients with other types of heart disease neither deep inspiration nor expiration produced any significant change in the slight bowing of the J-K segment and in no case did these procedures increase the angle to 8 degrees or more.

The most consistent pattern observed in the high-frequency ballistocardiogram was a relatively small K wave and a deep M wave (Table I, Fig. 1, *B*, *C*). This pattern was present in ten of the seventeen cases of aortic stenosis with or without incompetence. It was most commonly associated with a large J-K angle in the low-frequency ballistocardiogram. It occurred in seven of eleven such cases, but was only seen in two of six cases with a J-K angle of 7 degrees or less.

DISCUSSION

The angulation of the J-K segment of the low-frequency ballistocardiogram which was found to be present in a significant number of cases of aortic stenosis or combined aortic stenosis and incompetence has been attributed to aortic valvular stenosis as it was not observed in pure aortic incompetence due to syphilis. Such a contention was supported by other indirect evidence. The group of cases of aortic valvular disease with a large J-K angle, as opposed to those with a small angle, showed several features consistent with a predominance of aortic stenosis, viz., a small systolic and minute systolic force, a small pulse pressure, and the more frequent occurrence of a plateau and bisferiens type pulse. The two groups were similar in all other respects including loudness of murmurs, a diminution or absence of the second heart sound, the presence of a carotid shudder, and electrocardiographic and radiologic evidence of left ventricular enlargement.

The outwardly bowed or angulated J-K segment of the low-frequency ballistocardiogram appeared to be relatively specific to aortic stenosis. It was not observed in 200 tracings taken from patients with other types of heart disease including cases of syphilitic aortic incompetence. However, in some of these ballistocardiograms a slight degree of bowing of the J-K segment was seen and for this reason only an angle greater than 7 degrees has been considered significant. The average J-K angle in normal subjects was 1 degree and only two cases (4 degrees and 7 degrees) exceeded 3 degrees.

Angulation or bowing of the I-J segment can superficially resemble angulation or bowing of the J-K segment. We have observed it in seven out of eight cases of coarctation of the aorta, in some cases of mitral incompetence and transiently at the beginning of suspended respiration in cases of emphysema and cor pulmonale. The differentiation of angulation of the I-J from that of the J-K segment can be made by measurement of the time interval between the beginning of the Q or R wave of the electrocardiogram and the deflections of the ballistocardiogram. The average Q-J interval in normal subjects was 0.36 sec. with

a range of 0.30 sec. to 0.42 sec. Angulation of the I-J complex was considered to be present when this occurred on the upstroke of a complex corresponding in time to the J wave. Angulation of the J-K segment occurred on the downstroke of such a wave.

Jones[7] has considered that the measurement of the time intervals between the electrocardiogram and the deflections of the low-frequency ballistocardiogram are of value and has reported significant differences between young and old normal subjects and between the latter groups and patients with arteriosclerotic and hypertensive heart failure. These measurements were also found to vary with the presence or absence of congestive cardiac failure.

A comparison of the average values in the normal subjects with those of the patients with aortic stenosis with or without incompetence showed a shortening of the Q-H and Q-I times in the latter which could possibly be related to the reduction in the force of early systolic discharge observed in experimental aortic stenosis.[8] The prolongation of the H-I, I-J, H-J, and H-K times in the aortic stenosis series was compatible with the prolongation of systole observed in this condition.[10] The average Q-H and Q-I intervals in pure aortic incompetence were prolonged while the I-J, J-K, and H-K times were less than normal. Jones[7] has described similar findings in congestive cardiac failure. As past or present congestive failure was a feature of all our cases of aortic incompetence it was not possible to decide whether these findings were due to aortic incompetence or to congestive cardiac failure.

A tendency for the angulation of the J-K segment to become accentuated in deep inspiration in aortic stenosis was seen in many cases. It has been demonstrated that the stroke volume of the left ventricle decreases during inspiration while that of the right ventricle increases.[9,10] Our results indicate that a large J-K angle is more commonly found in cases with a small systolic force, and it is likely that the accentuation of the J-K angle is related to the reduction of left ventricular stroke volume during inspiration.

The genesis of the various deflections of the ballistocardiogram is at present poorly understood and any attempt at a detailed analysis of the changes observed in aortic stenosis would be premature. The predominant circulatory disturbance produced by aortic stenosis is reflected in the character of the arterial pulse and the factors responsible for this are the most likely cause of the ballistocardiographic abnormalities. Feil and Gilder[11] have demonstrated graphically the slow rise and late peak in the plateau pulse of aortic stenosis as well as the double peaked or bisferiens pulse found in some cases of combined aortic stenosis and incompetence. The late peak of the plateau pulse, the second peak of the bisferiens pulse, and the angulated J-K segment of the ballistocardiogram occur in late systole, and it is possible that the factors responsible for this phase of the plateau and bisferiens pulse are also the cause of the angulated J-K segment.

The high-frequency ballistocardiogram was characterized by a pattern showing an abbreviated and often slurred K wave and a deep M wave. The common association of this pattern with a large J-K angle in the low-frequency ballistocardiogram has been noted but the pattern of the high-frequency ballistocardiogram did not appear to be as specific for aortic stenosis as that described

in the low-frequency ballistocardiogram. A similar small K wave and deep M wave have occasionally been seen in normal records and were encountered in seven out of eight cases of coarctation of the aorta. These also occurred in some of the complexes of 15 per cent of the records of 200 cases with various types of heart disease.

SUMMARY

1. Low-frequency critically damped and high-frequency ballistocardiograms were analyzed in three cases of aortic stenosis and in fourteen cases of combined aortic stenosis and incompetence. These findings were compared with the ballistocardiograms of normal subjects and of patients with other types of heart disease including syphilitic aortic incompetence.

2. Angulation or bowing of the J-K segment of the low-frequency ballistocardiogram was greater than that observed in the control group in eleven of the seventeen cases of aortic stenosis and combined aortic stenosis and incompetence. This finding was attributed to the aortic stenosis in view of its absence in cases of pure aortic incompetence due to syphilis and other types of heart disease.

3. The degree of angulation of the J-K segment of the low-frequency ballistocardiogram correlated roughly with the extent of aortic valvular stenosis.

4. A small K wave and a deep M wave in the high-frequency ballistocardiogram were found in ten of the seventeen cases of aortic stenosis or combined aortic stenosis and incompetence. This pattern did not appear to be as specific for aortic stenosis as that observed in the low-frequency ballistocardiogram as it was also seen in some normal subjects and in patients with coarctation of the aorta and other types of heart disease.

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FAT TOLERANCE IN SUBJECTS WITH ATHEROSCLEROSIS: HEPARIN EFFECTS UPON LIPEMIA, LIPOPROTEINS, AND GAMMA GLOBULIN

Asher Woldow, M.D.,* James E. Chapman, M.D., and John M. Evans, M.D.

Washington, D. C.

One of us (A. W.),[1] measuring the degree and duration of lipemia following a standard fat meal, observed impaired fat tolerance in patients with coronary artery disease as compared to normal subjects. Hahn[2] and Weld[3] showed that small intravenous doses of heparin abolished alimentary lipemia in dogs. Swank and Wilmont[4] demonstrated by ultracentrifugation that the turbidity of lipemic serum was produced by chylomicrons made up of 97 per cent neutral fat. Anderson and Fawcett[5] confirmed the work of Hahn[2] and Weld[3] and suggested that the antichylomicronemic substance resulting from heparin injection was a heparin-phospholipid complex.

Several investigators[6-8] have presented evidence that blood lipids are transported as lipoprotein complexes. Turner and associates[9], analyzing ultracentrifuged normal human serum, found that the layers containing 66 per cent of lipids also contained about 60 per cent of the total protein largely in the form of globulin.

The present report summarizes further studies of fat tolerance in normal subjects and in patients with atherosclerosis and includes a consideration of the blood levels of lipoprotein and gamma globulin in response to a fat meal and to the intravenous injection of heparin.

MATERIAL AND METHODS

The subjects studied were selected on the basis of the presence of atherosclerosis in individuals free of the edema of heart failure or liver disease. All of the twenty-one test subjects (Table I) had unequivocal evidence of coronary artery disease. Twenty had sustained a myocardial infarction confirmed by the diagnostic pattern in the electrocardiogram and one presented angina pectoris

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From the Department of Medicine, The George Washington University School of Medicine, Washington, D. C.

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*Postdoctorate Research Fellow of The National Heart Institute, National Institutes of Health, United States Public Health Service.

with a positive Master's exercise test. All subjects with myocardial infarction were studied some time after the acute episode except one who was tested in the recovery period during hospitalization. The age range in the coronary group was twenty-eight to seventy-four years, with an average of fifty-five years, and included eight patients under fifty years of age and six patients under forty-five years of age.

The thirteen normal control subjects (Table II) were hospital personnel or other healthy individuals in whom there was no suspicion of atherosclerosis or primary liver disease. Selection on this basis necessarily excluded individuals in the older age groups where atherosclerosis may be latent. The age range of the controls was twenty-five to forty-eight years with an average of thirty-one years.

All studies were carried out after a ten-hour period of fasting. Following withdrawal of a 10 ml. blood sample into a plain test tube, the subject ate a standard fat meal of 200 ml. of 20 per cent sweet cream. While fasting continued, samples were collected similarly at three and five hours. In some of the studies, after removal of the five-hour sample, 25 mg. of heparin* were injected intravenously and a fourth sample obtained ten to fifteen minutes later from a vein of the opposite arm.

The blood samples were centrifuged at 3,000 r.p.m. for twenty minutes. The optical density of the serum was measured with a spectrophotometer† set at a wave length of 650 mμ. The serums were examined for lipemia turbidity (lipemia), for turbidity after treatment with buffered thymol, and for their content of gamma globulin. Thymol turbidity was determined by the method of Maclagan[10] as modified by Shank and Hoagland,[11] and gamma globulin by the method of Kunkel.[12] The lipemia turbidity was used as an index of large chylomicrons as shown by Swank and Wilmont.[4] The thymol turbidity procedure was employed as an approximate measure of lipoproteins. As reported by Maclagan,[10] the thymol precipitate contains 37.5 per cent protein, 32 per cent thymol, 16.5 per cent cholesterol, one-half esterified, and 8 per cent phospholipids. The Kunkel[12] technique yields largely gamma globulin from solution, but as Kunkel pointed out other proteins may influence the volume of the precipitate.

RESULTS

Fig. 1 presents graphically the averages of the lipemia turbidity after fat feeding in all of the twenty-one atherosclerotic subjects. In the normal or control subjects there are thirteen studies of lipemia turbidity and ten studies of thymol turbidity. At three hours after fat loading the averages of the lipemia and thymol turbidities were significantly higher in the coronary group than in the control group (Fig. 1.). At five hours higher levels of lipemia and thymol turbidity persisted in the coronary group, while in the control group the levels were returning toward fasting.

*The heparin was supplied in part through the courtesy of Eli Lilly and Company.

†The Coleman Junior Model spectrophotometer was used.

Table I. Descriptive Data and Optical Density Results in Subjects with Coronary Artery Disease

SUBJECT NO.	AGE	SEX	LIPEMIA TURBIDITY				THYMOL TURBIDITY				GAMMA GLOBULIN				COMMENT
			FASTING	3 HOUR	5 HOUR	POST-HEPARIN	FASTING	3 HOUR	5 HOUR	POST-HEPARIN	FASTING	3 HOUR	5 HOUR	POST-HEPARIN	
1	62	M	.0555	.1427	.1249		.0362	.0605	.0706						Old myocardial infarction
2	73	M	.0655	.2291	.5090		.0555	.0915	.1427						Old myocardial infarction
3	66	M	.0862	.2007	.4090		.0969	.1249	.2076						Old myocardial infarction
4	53	M	.0505	.5230	.2924		.0362	.1367	.1079						Old myocardial infarction
5	60	M	.0888	.1905	.1192	.0482	.0706	.0915	.0862	.0458					Old myocardial infarction
6	70	M	.0555	.0706	.1024	.0757	.0177	.0177	.0223	.0177					Old myocardial infarction
7	65	F	.1024	.1871	.5850	.5380	.0326	.0458	.1079	.1487					Old myocardial infarction
8	48	F	.0555	.3190	.1249	.0706	.0177	.0605	.0655	.0580	.0505	.0555	.0680	.0362	Old myocardial infarction
9	58	M	.0505	.0862	.1192	.0605	.0088	.0200	.0362	.0246	.0410	.0269	.0555	.0269	Old myocardial infarction

10	71	M	.0655	.2676	.3470		.0362	.0531	.0705	.0458	.0386	.0362	.0362	.0269	Old myocardial infarction
11	74	M	.0531	.1805	.1024						.0959	.0959	.0959	.0655	Old myocardial infarction
12	35	M	.0835	.1441	.1427		.0386	.0783	.0505						Old myocardial infarction
13	49	F	.0434	.2480	.2147		.0200	.0505	.0410	.0505	.0680	.0680	.0809	.0458	Old myocardial infarction
14	64	M	.0505	.1079	.1805	.0505					.0458	.0362	.0655	.0315	Old myocardial infarction
15	28	F	.0706	.2756	.2076	.1249	.0177	.0555	.0410	.0223	.0655	.0315	.0731	.0531	Old myocardial infarction
16	45	M	.0862	.3870	.2840		.0482	.1192	.1249						Old myocardial infarction
17	40	M	.0959	.2676	.0809	clear	.0410	.0410	.0223	.0155	.0783	.0835	.0809	.0605	Old myocardial infarction
18	64	M	.0555	.2282	.2218	.0505	.0458	.0706	.0655	.0410	.0200	.0410	.0339	.0269	Old myocardial infarction
19	55	M	.0458	.1192	.0809		.0223	.0362	.0292						Acute myocardial infarction
20	32	M	.0655	.2364	.4950		.0362	.0757	.1249	.0915	.0223	.0410	.0505	.0410	Angina pectoris
21	40	M	.0706	.3280	.2518		.0862	.1427	.1612						Subendocardial infarction
Average 55			.0653	.2269	.2286	.1183	.0382	.0691	.0796	.0475	.0547	.0557	.0680	.0445	

TABLE II. DESCRIPTIVE DATA AND OPTICAL DENSITY RESULTS IN CONTROL SUBJECTS

SUBJECT NO.	AGE	SEX	LIPEMIA TURBIDITY				THYMOL TURBIDITY		
			FASTING	3 HOUR	5 HOUR	POST-HEPARIN	FASTING	3 HOUR	5 HOUR
1	32	M	.0223	.0757	.1135		.0088	.0362	.0362
2	25	M	.0505	.1135	.0505		.0269	.0362	.0223
3	26	F	.0555	.1549	.0757		.0223	.0362	.0269
4	32	F	.0458	.1487	.0605		.0269	.0458	.0269
5	35	F	.0362	.0809	.1024		.0132	.0246	.0292
6	48	F	.0339	.1871	.0655		.0132	.0458	.0177
7	28	M	.0458	.0969	.2291	.0355	.0809	.1079	.1249
8	30	M	.0410	.1772	.1549	.0458			
9	27	F	.0315	.0605	.0555				
10	31	F	.0434	.1135	.0680				
11	36	M	.0482	.1580	.1192	.0458	.0177	.0315	.0269
12	26	F	.0339	.0835	.0580	.0315	.0132	.0315	.0269
13	27	F	.0458	.0783	.0655	.0410	.0269	.0269	.0362
Average	31		.0411	.1177	.0937	.0439	.0250	.0423	.0374

The results of the individual lipemia turbidity and thymol turbidity determinations for fasting, three-hour, and five-hour samples are plotted for each subject in Fig. 2*A* and Fig. 2*B*. The preponderance of higher values of optical density in the atherosclerotic subjects is clear cut although there is some overlapping with the controls. One subject, No. 7, icluded in the normal group presented elevated lipemia and thymol turbidities. He was known to have had infectious hepatitis two years previously and still has occasional minimal liver tenderness upon palpation. All liver function studies except the thymol turbidity were within normal limits in this subject.

It was observed in most instances that chronic passive congestion or primary liver disease reduced the degree of lipemia after fat loading. The fat tolerance was repeated serially from two to three times at intervals of six days to five months in seven coronary subjects and in no instance did the pattern of fat tolerance return to normal.

Fig. 3 illustrates the influence of the intravenous injection of 25 mg. of heparin upon lipemia turbidity in ten patients with coronary artery disease and in five normal subjects. The lipemia turbidity fell to approximately fasting levels in the five normal subjects tested. Of the ten subjects with coronary artery disease, the reduction in lipemia turbidity from the five-hour level was marked in nine and minimal in one.

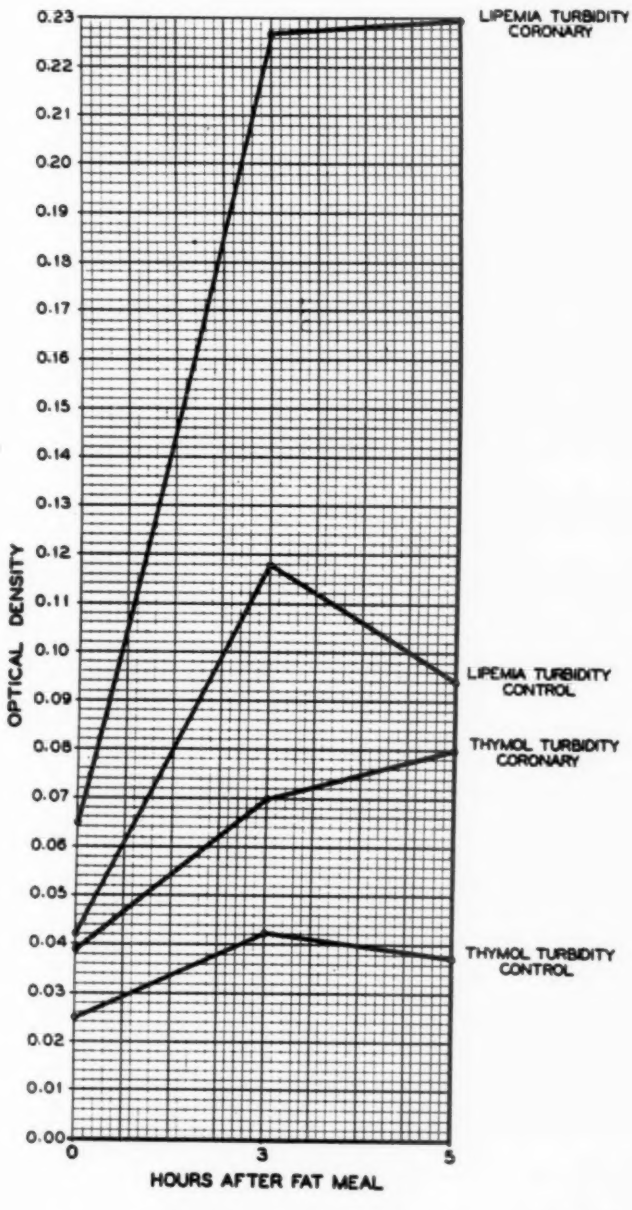

Fig. 1.—Averages of lipemia turbidity and thymol turbidity in coronary and control subjects.

The heparin effect upon thymol turbidity (Fig. 3) was similar in that there was well defined clearing in ten of the twelve subjects tested with coronary artery disease. In one subject the thymol turbidity was low at the fifth hour and essentially unchanged after heparin. In the twelfth subject there was no significant change in either thymol or lipemia turbidity after heparin.

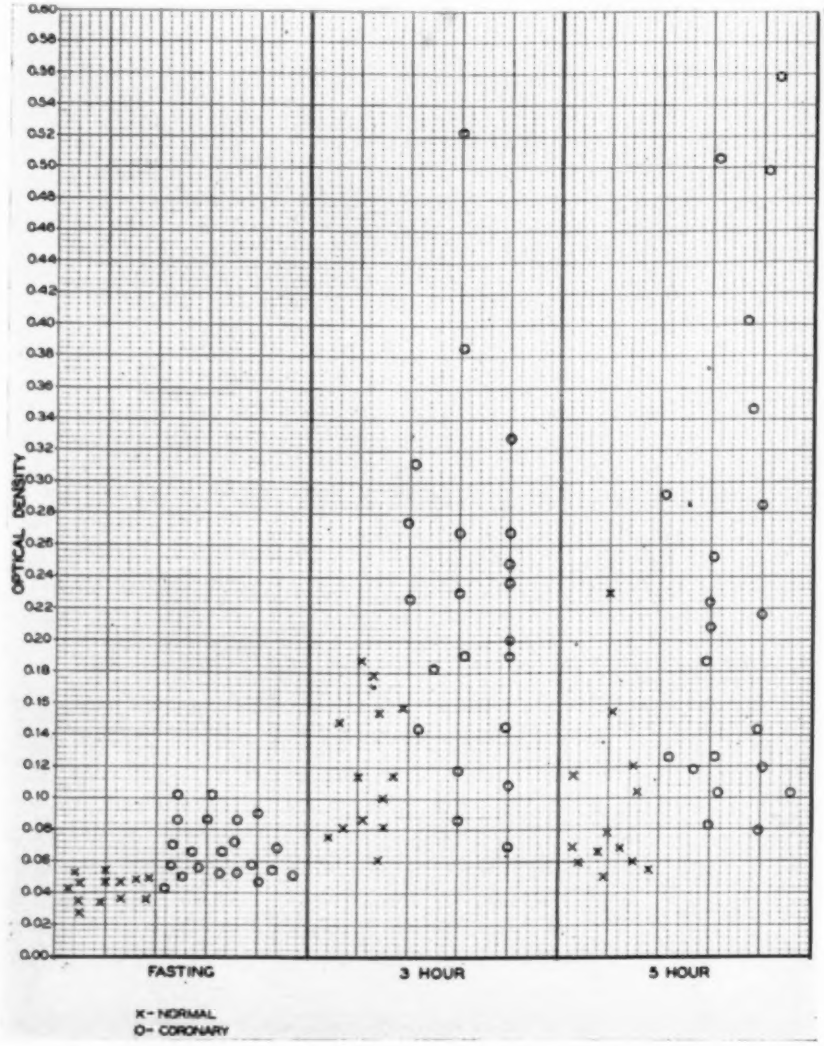

Fig. 2*A*—Optical density determinations of lipemia turbidity before and after fat meal in coronary and control subjects.

Fig. 3 also shows the response of gamma globulin to fat loading and to an intravenous injection of 25 mg. of heparin in the eleven coronary subjects thus studied. In four of the eleven, gamma globulin levels were approximately the same in the fasting, three- and five-hour specimens; in the remaining seven patients

there was no definite pattern to the minor changes that occurred. However, in all eleven subjects injection of heparin was followed by a significant drop in gamma globulin concentration. In nine of eleven subjects the globulin fell to or below fasting levels, and in all instances was lower than the five-hour concentration.

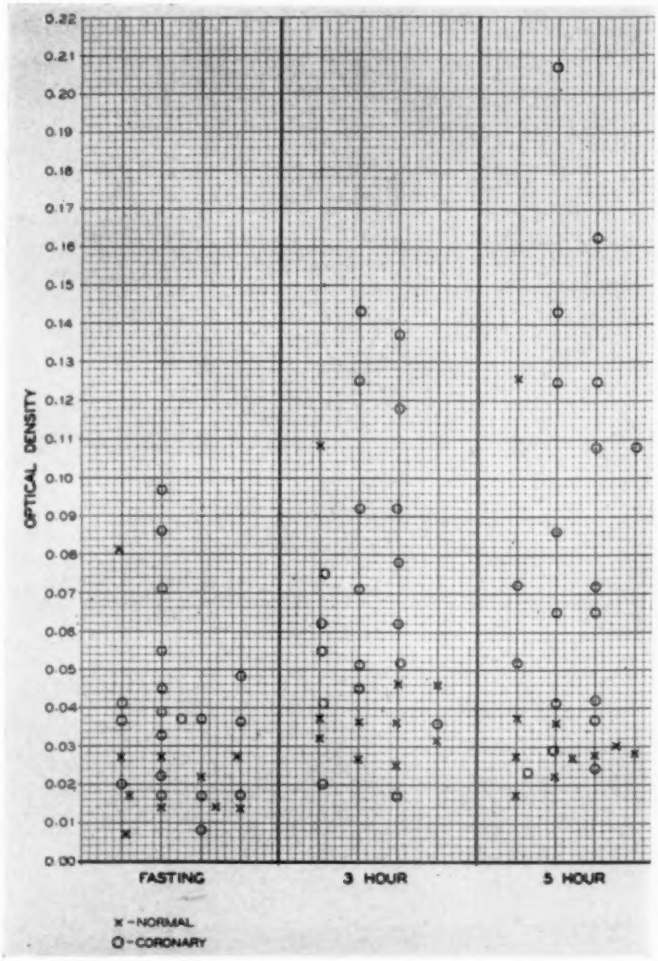

Fig. 2*B*.—Optical density determinations of thymol turbidity before and after fat meal in coronary and control subjects.

The in vitro attempts to reproduce the heparin effect upon lipemia and thymol turbidity were unsuccessful as there was no significant change in optical density. However, the gamma globulin precipitate was promptly cleared in all instances by the addition of 1.0 mg. of heparin to approximately 6.0 ml. of precipitate.

DISCUSSION

The present observations confirm the studies of other workers[1,14,15] who have noted an increase in the degree and duration of alimentary lipemia in subjects with atherosclerosis in comparison with normal controls. In the investigation

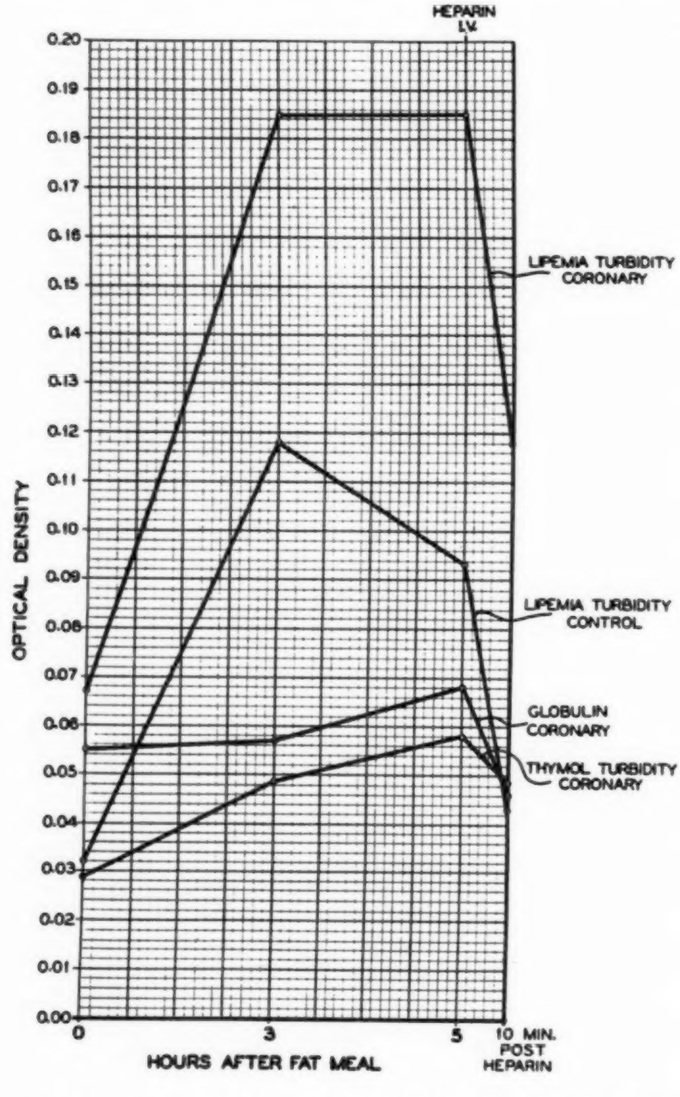

Fig. 3.—The response of lipemia turbidity, thymol turbidity and gamma globulin to intravenous heparin.

of Schwartz and associates[1] the group with coronary atherosclerosis was composed of patients recovering from acute myocardial infarction in whom studies were done within eight weeks from onset of the attack. The subjects herein reported include nineteen patients with remote myocardial infarction (one to five years),

one patient recovering from acute myocardial infarction, and one patient with angina pectoris confirmed by the Master exercise test. The similarity of the lipemia pattern at different stages of coronary artery disease indicates a common defect in fat transport and excludes the possibility that the pattern is associated only with acute myocardial infarction.

Since Swank and Wilmont,[4] by ultracentrifugation and dark-field microscopy, showed that chylomicrons produce the turbidity of lipemic serum it was considered that serum turbidity measurements by optical density would be a satisfactory means of quantitating chylomicrons (lipemia). Subjects with atherosclerosis generally show persistence of lipemia at the fifth hour after a fat meal while in normal subjects the degree of lipemia is returning toward the fasting level. It is also apparent that as lipemia increases at three and five hours there is more precipitatable lipoprotein (thymol turbidity) in the atherosclerotic group than in the normal group.

If the defect of fat transport in atherosclerosis is concerned with the inability of chylomicrons to combine with protein as lipoprotein complexes, the atherosclerotic subject should then show lower lipoprotein levels after fat loading in comparison with normal subjects. In the latter group, however, it is apparent that the same fat load is transported with less lipemia, as well as less precipitatable lipoprotein. This would seem to indicate that the normal regulating factors influence the levels of both lipemia and lipoprotein.

In normal subjects it is noted that lipemia is receding spontaneously in parallel with a decline in lipoprotein at five hours after fat loading. The injection of heparin at the fifth hour induces prompt further clearing of the serum to or below the fasting level. These observations suggest that the introduction of heparin accelerates and intensifies a physiologic reaction which is already in progress.

In coronary artery disease it is also apparent that intravenous heparin clears lipemia and simultaneously decreases precipitatable lipoproteins after fat loading. Therefore it would seem that heparin initiates a response at five hours in the coronary group which has begun spontaneously at three hours in the normal group. Accordingly it is confirmed that heparin has not only the "antichylomicronemic" action of Anderson and Fawcett[5] but also influences the function of lipoproteins in fat transport by reducing the concentration of precipitatable lipoprotein. Thus, in subjects with atherosclerosis, injection of heparin induces more normal handling of the alimentary fat load.

Block and associates[13] have recently reported studies of the clearing effect of heparin upon alimentary lipemia in subjects with atherosclerosis. It was their conclusion that male atherosclerotic subjects showed much less clearing of plasma in comparison with normal men and women.

Turner and associates,[9] analyzing ultracentrifugates of normal human serum, found that approximately 66 per cent of the lipids and 60 per cent of the proteins were present in the same density zones. The proteins were chiefly in the form of globulin. These workers concluded that much of the globulin of these zones was the protein constituent of lipoprotein. Cohn and associates[16] have determined that the globulin fractions of the serum proteins contain large amounts of cho-

lesterol, phospholipids and possibly other lipids. Kunkel[12] detected a marked increase in beta globulin in sera with elevated lipids. In previously heparinized plasma Graham and associates[8] demonstrated a principle which is active in clearing lipemic serum and by ultracentrifugation located the "active principle" in the globulin region. Our data show that with atherosclerosis there is uniformly less gamma globulin following heparin injection, the reduction occurring simultaneously with the clearing of lipemia and the decrease in precipitatable lipoprotein.

The occurrence of increased lipemia and precipitatable lipoprotein following fat loading in humans with atherosclerosis suggests that lipoprotein may be concerned with the defect in neutral fat transport. The action of heparin in clearing lipemia and reducing precipitatable lipoproteins, thus returning serum fat distribution towards normal, indicates that a deficiency of heparin or a heparin-like substance may be associated with abnormal fat transport. The alteration of gamma globulin noted by us and the elevated beta globulin noted by Kunkel[12] and Eder and Russ[17] in patients with lipemia would emphasize that several globulin fractions may play a part in fat transport.

The decline in gamma globulin concentration after heparin both in vivo and in vitro may indicate that a globulin-heparin reaction occurs simultaneously with clearing of lipemia and that globulin has a role in maintaining normal physical and chemical distribution of neutral fats. Anfinsen and associates,[18] in a recent comprehensive study, elaborated a complex theory to explain the heparin effect on lipemia. They reported the presence of a plasma "co-protein" which served an acceptor function in the clearing of turbidity and shifts of lipoproteins. These observations emphasize the need for further investigation of the role of plasma proteins in fat transport and in atherosclerosis.

CONCLUSIONS

1. The occurrence of an increased degree and duration of alimentary lipemia is confirmed in subjects with coronary artery disease in comparison with normal subjects. At three hours after a fat meal precipitatable lipoproteins and lipemia are higher in subjects with coronary artery disease than in normal subjects.
2. At five hours after fat loading, the levels of lipemia and lipoprotein are returning toward fasting in normal subjects while remaining elevated in subjects with coronary artery disease.
3. It appears that heparin or a heparin-like substance may be an active factor in normal fat transport, since intravenous heparin accelerates clearing of lipemia in normal subjects and initiates the response in subjects with coronary artery disease.
4. The reduction in gamma globulin concentration by heparin both in vivo and in vitro suggests that a heparin-globulin reaction may occur in association with clearing of lipemia.
5. The possible implications of these observations are discussed in relation to fat transport and atherosclerosis.

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RHEUMATIC HEART DISEASE IN NATIVE-BORN FLORIDIANS AND NON-FLORIDIANS

An Analysis of the Birthplace of 1,909 Outpatient Records

Milton S. Saslaw, M.D., Bernard D. Ross, M.D., Ph.D., and F. A. Hernandez, M.D.

Miami, Fla.

SURVEYS of school populations in various localities have shown a lower incidence of rheumatic heart disease in Florida, southern Arizona, and Redlands, California, than in more northern communities. Rates per 1,000 reported in northern climates are: 25.0 to 38.5, in New Haven, Connecticut[1]; 45.0, in Montana and Wyoming.[2] Rates per 1,000 reported in southern climates: 3.8, in Redlands, California[3]; 5.0, in southern Arizona[2]; 5.0, in Dade County, Florida[4]; and 3.8, in Pensacola, Florida.[5]

As the patients seen in our Outpatient Clinic come from northern areas, as well as Florida, we felt that our records, heavily weighted with cardiac suspects, might furnish comparative data concerning rheumatic heart disease in native-born Floridians and non-Floridians.

MATERIALS AND METHODS

The records of 1,936 patients examined at the Outpatient Clinic of this hospital, from April 8, 1946, through Nov. 18, 1952, were analyzed according to age, sex, color, diagnosis, and birthplace. All were suspected of having heart disease and had been referred to the clinic by private physicians, hospitals, schools, and social service agencies.

A careful history, physical examination, laboratory tests (including urinalysis, complete blood count, sedimentation rate), roentgenograms, electrocardiogram, and fluoroscopy were done in each case. Cardiac catheterization was performed when indicated.

Criteria of the American Heart Association[6] were followed in diagnosing heart disease of both congenital and rheumatic origin. We applied the term "rheumatic state" to all those with active and inactive rheumatic heart disease, active rheumatic fever, and a history of rheumatic fever but no demonstrable cardiac involvement.

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Birthplaces were classified as Florida and non-Florida. Eight cases were excluded from the study because of incomplete records, and six, because a definite diagnosis could not be made. Also omitted from the statistical analysis, because of small numbers, were thirteen miscellaneous cases diagnosed as follows:

Tuberculous pericarditis	1
Congenital heart disease and rheumatic heart disease (coexistent)	7
Diphtheritic myocarditis	1
Still's disease with heart involvement	1
Acute nephritis with cardiac complications	1
Arteriosclerotic heart disease	1
Arteriovenous fistula	1

Of the remaining 1,909 records, 1,540 were in the school age group of 5 through 17 years, 266 were under 5 years of age, and 103 were 18 and over.

Inasmuch as 80 per cent of the clinic patients were of school age, we attempted to determine to what extent they were representative of the total Dade County school population with respect to sex, color, and birthplace. We therefore analyzed 1,205 randomly selected* records of the approximately 80,000 children attending the grade and high schools of Dade County, Florida.

RESULTS

The outpatient and school groups were essentially the same with respect to sex, color, and birthplace (Table I). Males slightly predominated in all groups. Whites outnumbered Negroes over 5 to 1 in all groups. More than one-half in each group were born outside Florida.

Table II presents a breakdown of the diagnosis, age, color, and birthplace of the outpatients. The ratio of Floridians to non-Floridians was: 1.5 to 1 in those under 5 years; 1 to 1.9 in those 5 through 17 years; 1 to 4.8 in those 18 years and over; and 1 to 1.4 in all the age groups.

Analysis of the data shows that both the rheumatic state and rheumatic heart disease were more prevalent in white non-Floridians than in white Floridians, depending on the age group as follows:

Whites: Under 5 years: The rheumatic state occurred four times more often in the non-Floridians, 13.4 per cent versus 3.3 per cent in the Floridians. There were no cases of rheumatic heart disease in Floridians, and 4.1 per cent in non-Floridians.

Five through 17 years: The rheumatic state was twice as frequent in the non-Floridians, 34.9 per cent versus 16.6 per cent in the Floridians. Rheumatic heart disease was four times as frequent in the non-Floridians, 13.2 per cent versus 3.5 per cent in the Floridians.

Eighteen years and over: The number in this group was too small to permit any definitive conclusion. However, 4.6 times as many non-Floridians were in the rheumatic state, 57.9 per cent versus 12.5 per cent Floridians; 4.3 times as many non-Floridians had rheumatic heart disease, 53.9 per cent versus 12.5 per cent Floridians.

*School records are maintained alphabetically in files of approximately 2,000 individual record cards. Our outpatients 5 through 17 years old were subdivided year by year. In the school study, we included every fifteenth card in every third file, until the number for each age equaled that in our outpatient records. Thereafter, cards falling into that age group or any other completed age group were omitted. This method of sampling yielded an age distribution identical with that in our outpatient records of school age, which at the time the school records were analyzed totaled 1,205.

TABLE I. SEX, COLOR, AND BIRTHPLACE OF SCHOOL AND OUTPATIENT GROUPS

GROUP	TOTAL	SEX				COLOR				BIRTHPLACE			
		MALE		FEMALE		WHITE		NEGRO		FLORIDA		NON-FLORIDA	
		NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
School	1,205	616	51.1	589	48.9	1,011	83.8	194	16.2	561	46.5	644	53.5
Outpatients (School Age)	1,540	854	55.5	686	44.5	1,314	85.3	226	14.7	613	39.8	927	60.2
Total Outpatients	1,909	1,058	55.4	851	44.6	1,653	86.6	256	13.4	804	42.1	1,105	57.9
Total School Population	79,516	40,781	51.3	38,735	48.7	66,470	83.6	13,046	16.4	—	—	—	—

TABLE II. DIAGNOSIS, AGE, COLOR, AND BIRTHPLACE OF 1,909 OUTPATIENTS

GROUP	UNDER 5 YEARS									5 THROUGH 17 YEARS								
	FLORIDA			NON-FLORIDA			TOTAL			FLORIDA			NON-FLORIDA			TOTAL		
	W	N	T	W	N	T	W	N	T	W	N	T	W	N	T	W	N	T
No. Outpatients	150	19	169	97	0	97	247	19	266	459	154	613	855	72	927	1314	226	1540
Rheumatic state (%)	3.3	5.3	3.6	13.4	0.0	13.4	7.3	5.3	7.1	16.6	10.4	15.0	34.9	11.1	33.0	28.5	10.6	25.8
Rheumatic heart disease only (%)	0.0	0.0	0.0	4.1	0.0	4.1	1.6	0.0	1.5	3.5	5.8	4.1	13.2	6.9	12.7	9.8	6.2	9.2
Congenital heart disease (%)	63.3	57.9	62.7	39.2	0.0	39.2	53.8	57.9	54.1	21.8	22.7	22.0	14.6	27.8	15.6	17.1	24.3	18.2
No heart disease (%)	33.4	36.8	33.7	47.4	0.0	47.4	38.9	36.8	38.8	61.6	66.9	63.0	50.5	61.1	51.4	54.4	65.1	56.0

GROUP	18 YEARS AND OVER									TOTAL ALL AGES								
	FLORIDA			NON-FLORIDA			TOTAL			FLORIDA			NON-FLORIDA			GRAND TOTAL		
	W	N	T	W	N	T	W	N	T	W	N	T	W	N	T	W	N	T
No. Outpatients	16	6	22	76	5	81	92	11	103	625	179	804	1028	77	1105	1653	256	1909
Rheumatic state (%)	12.5	16.7	13.6	57.9	20.0	55.6	50.0	18.2	46.6	13.3	10.1	12.6	34.5	11.7	32.9	26.5	10.5	24.4
Rheumatic heart disease only (%)	12.5	16.7	13.6	53.9	20.0	51.9	46.7	18.2	43.7	2.9	5.6	3.5	15.4	7.8	14.8	10.7	6.3	10.1
Congenital heart disease (%)	68.8	50.0	63.6	25.0	20.0	24.7	32.6	36.4	33.0	33.0	27.4	31.7	17.7	27.3	18.4	23.5	27.3	24.0
No heart disease (%)	18.7	33.3	22.8	17.1	60.0	19.7	17.4	45.4	20.4	53.7	62.5	55.7	47.8	61.0	48.7	50.0	52.2	51.6

W = white, N = negro, T = total.

Negroes: There was no significant difference in either the rheumatic state or rheumatic heart disease, referable to birthplace, in the 5 through 17 age group. The numbers of Negroes under 5, and 18 and over, were too small to permit evaluation.

Congenital heart disease figures showed:

Under 5 years: About 60 per cent of both white and Negro Florida-born children under 5 years of age seen in our clinic had congenital heart disease. This figure fell to 40 per cent in the white non-Floridians. There were no Negro non-Floridians in this age group with congenital heart disease.

Five through 17 years: The white Floridians had 1.5 times as much congenital heart disease as the non-Floridians. The Negro rate was approximately the same regardless of birthplace.

Eighteen years and over: Here, again, the total numbers were too small to justify a conclusion.

DISCUSSION

Florida, in contrast to northern states, has a relatively low rheumatic fever and rheumatic heart disease rate. Among all the states, it ranked sixth lowest from 1939 to 1941, in deaths from acute rheumatic fever and other heart diseases in children despite the inclusion in these statistics[7] of non-Florida-born rheumatic patients who may have contracted their infections elsewhere. The present study of records, heavily weighted with children suspected of having heart disease, confirms previously reported[4,5] low rates of rheumatic heart disease in random samples of Florida-born school children.

The findings for our white patients, as a whole, are in accord with White's statement: "Climate appears to be an important factor in the incidence both of the rheumatic infection and of the rheumatic type of heart disease. . . . In the northern part of the United States the rheumatic infection and its permanent involvement of the heart are five times more frequent than in the southernmost part of the country."[8] We found that 5.3 times as many white non-Floridians as Floridians had rheumatic heart disease; 2.6 times as many were in the rheumatic state. The relatively lower frequency of rheumatic heart disease in comparison to the rheumatic state may well be a reflection of less severe illness in Floridians, attended by fewer cases with cardiac damage. It has been the experience of two of the authors, in private practice over a period of at least eight years in Miami, that acute rheumatic fever does not present the typical picture. Polyarthritis, one of the chief distinguishing features of the disease, was observed in only one case, and heart damage was uncommon.

The lower rate of rheumatic heart disease in our white Floridians may be due to two factors: first, our non-Floridian figures may be weighted with an undue number of rheumatic patients, who have migrated to Florida because of the general belief that its subtropical climate is beneficial to the rheumatic infection and its cardiac complications. Second, the disease may actually be less prevalent in the state of Florida, as indicated by our present findings and those previously reported.[4,5]

Negroes, born in Florida, in contrast to the white patients in our study, did not show lower rheumatic heart disease and rheumatic-state rates, when compared with non-Floridian Negroes. Rheumatic infection was essentially the same in both groups, regardless of birthplace. This was evident in the 5 through 17 age

group, where Floridian Negroes outnumbered non-Floridians 2 to 1. No conclusion can be drawn from the other two age groups, for there were no non-Floridian Negroes under 5 years of age, and only five, 18 years and over. Possible explanations of the similarity in rheumatic rates in Floridian and non-Floridian Negroes in our study are:

1. Susceptibility of the Negro to rheumatic heart disease may be such that climate fails to affect the rate of infection.

2. Socio-economic factors may influence the incidence and detection of rheumatic heart disease in Negroes.

3. Only one third of the Negroes 5 through 17 years of age were non-Floridians. This would seem to indicate that the Negro does not migrate to Florida as readily as whites in the same age group.

In our analysis, we arbitrarily grouped our patients as Floridians and non-Floridians. The northern boundary of the state of Florida at 31° N. latitude was considered the dividing line. As the number of patients born south of the thirty-first parallel, outside of Florida, was too small to warrant separate evaluation and did not significantly affect our figures, the thirty-three subjects concerned were included in the non-Floridian group. Of interest is the fact that there were eight Puerto Ricans, six of whom were in the rheumatic state.

The large number of Floridians under 5 years with congenital heart disease reflects the tendency of such patients to utilize the diagnostic facilities of our institution. Almost one-half of all the white Floridian patients with congenital heart disease were in this group. The small number of non-Floridians in this age group can be explained in two ways:

1. As the very severe cases of congenital heart disease do not survive beyond the first or second year of life, comparable native-born Floridians would be more likely to be seen at our clinic than those born elsewhere.

2. In general, there is less of a tendency for families with children under 5 years of age to migrate into Florida. The under 5 age group was the only one in which Floridians outnumbered non-Floridians.

The seemingly higher rate of congenital heart disease in Floridians 18 years and over may be explained, in part, by the fact that in our clinic patients over 18 are seen only when cardiac surgery or catheterization is contemplated. Another factor responsible may be that adults with congenital heart lesions are less likely to migrate to Florida for its beneficial climate than those with rheumatic lesions.

The similarity in sex, color, and birthplace between the statistics of our outpatients and those of the school population, would indicate that our findings are applicable to the entire childhood population of this area. The present survey confirms the previously reported[4,5] low incidence of rheumatic heart disease in native-born Floridians and provides further evidence that the rheumatic state and rheumatic heart disease are relatively infrequent in Florida-born children, as compared with those born elsewhere.

SUMMARY

1. Records of 1,909 patients of the Outpatient Clinic of the National Children's Cardiac Hospital, Miami, Florida, were studied to determine the

relative incidence of rheumatic heart disease in those born in Florida, as against those born outside of Florida.

2. The northern boundary of the state of Florida at 31° N. latitude was taken as an arbitrary dividing line.

3. Control analysis of records of children 5 through 17 years of age enrolled in the Dade County school system indicated that the outpatient records were comparable to the control records as to sex, color, and birthplace. More than one-half in each group were born outside of Florida.

4. Rheumatic heart disease was 5.3 times more prevalent in white non-Floridians.

5. The "rheumatic state" was diagnosed 2.6 times more frequently in non-Floridians than in Florida natives. This may signify less severe illness and fewer cardiac complications because of the favorable subtropical Florida climate.

6. In Negroes, the difference between Floridians and non-Floridians as regards rheumatic heart disease and the rheumatic state was not apparent. The factors contributing to this are discussed.

7. The present study of records weighted heavily with children suspected of having heart disease confirms previously reported[4,5] low rheumatic heart disease rates in random samples of Florida-born school children.

8. Possible explanations are offered for the lower rheumatic infection rate in Floridians.

9. The findings provide additional indirect evidence of the favorable effect of Florida's subtropical climate on rheumatic fever and its cardiac complications.

10. Variations in the congenital heart disease rates in Floridians and non-Floridians in this study are discussed.

The authors wish to express their appreciation to the Attending Medical Staff of the National Children's Cardiac Hospital, Miami, Fla., for their participation in the examinations on which the records in this report are based.

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EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE

A Review of the Literature and Report of 6 New Cases

Henning Gøtzsche, M.D.,* and Walther Falholt, M.D.

Copenhagen, Denmark

In more recent years the rare Ebstein's anomaly of the heart[5] has gained a certain interest through clinical similarity to certain other congenital malformations of the heart, especially Morgagni's syndrome (pulmonic stenosis combined with interatrial septal defect). The progress of recent years has made this differential diagnosis possible during life.

In Ebstein's anomaly there is a malformation of the right atrioventricular ostium. In most cases the leaflets of the tricuspid valve are displaced towards the apex of the heart and usually malformed, too. In other cases there is only a malformation of the normally inserting valves, which are large, thin, irregular, and may be defective, with coarse attachments to the adjacent ventricular wall. From a physiologic point of view the right ventricle is divided into a thin-walled part, incorporated into the right atrium, and a small functioning right ventricle with decreased ability to transport blood from the right atrium to the pulmonary artery. In some cases the anomaly also produces a tricuspid insufficiency. The low output of the right ventricle, compared to that of the left, explains the veno-arterial direction of the shunt in the cases associated with an interatrial septal defect or patent foramen ovale.

As Ebstein's anomaly is very unusual, it seems reasonable to give a short review of the literature. Since our aim is to discuss the possibility of establishing the intravitam diagnosis of Ebstein's disease in the light of modern methods of investigation, our review of the literature has been limited to those cases where a description of the electrocardiographic and/or roentgenologic findings is available, giving a total of sixteen† earlier cases.[1,2,4,6-8,10-13,15] The first case included is that of Yater and Shapiro.[15]

Yater and Shapiro[15] have given a review of earlier cases. Since their report only two cases are known by us to be without roentgenologic and electrocardiographic examination,[9,14] and one report has not been available to us.[3]

From the University Medical Clinic B, Rigshospitalet, Copenhagen, Denmark. Chief: Professor Erik Warburg, M.D.

Received for publication Oct. 8, 1953.

*Now Cardiologist, Municipal Hospital, Århus, Denmark.

†Since the preparation of this manuscript three additional cases have been reported by J. C. Broadbent, E. H. Wood, H. B. Burchell and R. L. Parker: Proc. Staff Meet., Mayo Clin. **28**:79, 1953.

CLINICOROENTGENOLOGIC FINDINGS

The diagnosis of Ebstein's anomaly has been made in vivo in five out of the sixteen cases reviewed in this paper. In the other eleven cases the diagnosis has been revealed on autopsy. Out of the total of sixteen cases, eleven are females and five males. One patient died at 8 months of age, because of intercurrent disease.[4] One patient, 5 years of age, died during operative attempt for the cardiac anomaly.[6] In the other instances the age at death varied from 10 to 53 years. In the cases, where the diagnosis was made during life the patients were from 13 to 34 years of age.

The symptoms of the 16 reviewed cases are seen in Table I.

TABLE I

		EARLIER CASES	OWN CASES	TOTAL
Dyspnea	present	14	6	20
	not mentioned	2	—	2
Paroxysmal tachycardia		2	—	2
Fainting spells		3	1	4
History of rheumatic fever		1	1	2
Cyanosis	present	13	4	17
	not mentioned	1	—	1
No murmurs		2	—	2
Systolic murmur		14	6	20
Quality of syst. murmur	rough	7	5	12
	soft	3	1	4
	not mentioned	4	—	4
Intensity of syst. murmur	loud	6	2	8
	moderate or faint	1	4	5
	not mentioned	7	—	7
Maximum of syst. murmur	3rd-4th left intercostal space	5	2	7
	lower precordium	3	3	6
	left chest posteriorly	1	—	1
	max. not stated	5	—	5
Diastolic murmur		8	3	11
Maximum in	early diastole	1	1	2
	mid-diastole	4	—	4
	late diastole	1	2	3
Audibility of diast. murmur	lower precordium	6	3	9
	whole precordium	2	—	2
Gallop rhythm	triple rhythm	5	3	8
	quadruple rhythm	1	1	2

Cardiac complaints were found in all patients. Dyspnea was a constant symptom. Two patients had paroxysmal tachycardia, which in one of the cases was the only complaint. A history of rheumatic fever was found in a single case. Some cardiac symptoms, such as palpitations, fatigue, precordial pain, and squatting, that presumably have not been systematically mentioned in the records, are not included in the table.

The most important clinical findings will be seen in Table I and here the sporadically mentioned signs are also omitted. Acyanotic cases are extremely rare. In all cyanotic cases the presence of an interatrial septal defect has been proved, either at autopsy, by cardiac catheterization, or angiocardiography.

The cyanosis in Ebstein's disease is thus undoubtedly caused by a veno-arterial shunt through an interatrial septal defect, which is in agreement with the results of measuring the arterial oxygen saturation at rest and during exercise as mentioned later. Clubbing of the fingers has been reported in only two instances.

Clinical enlargement of the heart is frequently mentioned, bulging of the precordium and palpable thrill only occasionally. Estimations of the second pulmonic and aortic sounds have been given in a few instances. Murmurs are more constantly mentioned, and they are summarized in Table I. No murmurs were found in two cases, namely, the youngest and oldest patient, aged 8 months and 53 years, respectively. In all the other cases there was a systolic murmur, most frequently rough and loud. In the cases where a distinct maximum intensity of the murmurs is established, this was found at or caudad of the third left intercostal space. Diastolic murmurs are common and are usually audible in the lower precordial area. In more than one third of the cases gallop rhythm was heard, usually a triple rhythm.

TABLE II

	EARLIER CASES	OWN CASES	TOTAL
Electrocardiography			
Right bundle branch block	12	5	17
Probably right bundle branch block, (left-axis deviation)	1	—	1
Right-axis deviation without bundle branch block	2	—	2
Wolff-Parkinson-White block	—	1	1
Low voltage of QRS	2	—	2
T-wave changes	2	2	4
Nodal rhythm, ventricular premature beats, or paroxysmal tachycardia	3	1	4
Prolonged P-Q interval	3	2	5
Enlarged P-waves	6	4	10
Roentgenologic findings			
Cardiothoracic index: stated to be increased	6	—	6
Cardiothoracic index: greater than 0.60	8	3	11
Cardiothoracic index: greater than 0.50	1	2	3
Cardiothoracic index: normal	1	1	2
Left cardiac border convex and elevated	11	4	15
Hilar vascular markings: normal	8	—	8
Hilar vascular markings: faint	4	6	10
Hilar vascular markings: not mentioned	4	—	4
Pulmonary arch: no prominence	14	3	17
Pulmonary arch: prominence	1	3	4
Pulmonary arch: not mentioned	3	—	3

The electrocardiographic findings are summarized in Table II. A definitely normal electrocardiogram was not found in any case. Right bundle branch block is the rule, in some cases combined with large P waves or delayed atrioventricular conduction. T-wave changes and abnormal rhythms are seldom found. There was one case with a history of paroxysmal tachycardia and one verified case.

The roentgenologic findings are given in Table II. Estimates of the size of the heart chambers and the density of the peripheral lung fields are omitted.

Table III. Catheterization Findings in Ebstein's Disease

CASE	RIGHT ATRIUM ESTIMATED AT CATHETERIZATION	CATHETERIZATION OF AN INTERATRIAL SEPTAL DEFECT	ARTERIOVENOUS SHUNT AT CATHETERIZATION	ARTERIAL OXYGEN SATURATION		PRESSURE IN		
				AT REST	DURING EXERCISE	PULMONARY ARTERY	RIGHT VENTRICLE	RIGHT ATRIUM
Reynolds, 1950	Huge	+	No	79				
Baker et al., 1950, Case 1	Enormous	+	No	75				
Baker et al., 1950, Case 2	Enormous	+	No	93				
Engle et al., 1950, Case 2	?	+	No	66	31			
Van Lingen et al., 1952, Case 1	?	–	Interventricular septal defect*	87	76	22/10	22/4 (7/4**)	7/4
Van Lingen et al., 1952, Case 2	?	–	Interatrial septal defect	69	55	22/10	22/8 (mean 9½**)	
Goodwin et al., 1953, Case 2	Large	–	No	88				2
Present Case 1	Enormous	–	Interatrial septal defect	87	80	14/8	18/2	7/4
Present Case 2	Large	+	No	89	84	16/4	27/2	8/2
Present Case 3	Huge	–	No	93	92	17/10	22/0	15/3
Present Case 4	Enormous	+	No	89	75		25/0	8/1
Present Case 5	Huge	–	No	96	92	15/8	15/0	2
Present Case 6	Large	–	Interatrial septal defect	90	75	16/6	24/2	3

* Estimated from the oxygen figures (not mentioned by the authors)
**Proximal part of the right ventricle

The findings cited are very consistent. Generally, the patients present an enlarged heart with a long bulging left border, forming one big elevated convexity, together with normal or faint hilar vascular markings and a not (or but slightly) bulging main stem of the pulmonary artery ("pulmonary arch"). As a rule, the breadth of the heart is maintained to be increased in the left anterior oblique position, too. Pulsation of the heart is only sporadically mentioned. One author[2] reports rapid, irregular pulsations of the heart by kymography. Reynolds,[10] and Engle and associates[6] (Case 1) state that the pulsation of the right heart border is diminished, and Goodwin and associates[7] (Case 2) state that the pulsations are not pronounced. Only in one publication[8] have the authors attempted a more specific evaluation, and they found diminished pulsation of the heart borders in the anteroposterior position, as compared to a vigorously or normally pulsating left ventricle in the left anterior oblique position.

In the column to the right in Tables I and II the clinical, electrocardiographic and roentgenologic findings of our own six cases are cited. Generally they are consistent with those of the literature. The most interesting exception is the Wolff-Parkinson-White block in one of our cases.

SPECIAL METHODS OF INVESTIGATION

Cardiac catheterization was performed in seven of the cases reviewed (Table III). In three cases information is given of gross enlargement of the right atrium. An additional interatrial septal defect has been directly catheterized in four cases, and in two other cases the evidence of an arteriovenous shunt between the atria indicated the presence of an interatrial septal defect. In one of the cases[8] an arteriovenous shunt to the right ventricle apparently was present, as evidence of an associated interventricular septal defect. In three instances the arterial oxygen saturation had been followed during exercise, and in all these cases a decrease had been registered.

The literature seems to show that the catheterization of the functioning part of the right ventricle and particularly the pulmonary artery often is difficult. Catheterization of the right ventricle and pulmonary artery has only been managed in two out of the seven catheterized cases. In the three cases, where information is given on the pressure in the right atrium this has been found slightly increased or normal.

Of our six cases catheterization of the pulmonary artery was successful in five instances. In our Case 4 only the functioning part of the right ventricle was catheterized. The systolic pressure in the pulmonary artery was in all cases slightly lower than that of the right ventricle, though the pressure in the ventricle did not exceed the limit of normal right ventricular pressure (30 mm. Hg, systolic). An associated interatrial septal defect was directly catheterized in two of our cases, and in two cases an arteriovenous shunt indicated the presence of an interatrial septal defect. In two cases no evidence was found of interatrial septal defects as blood samples did not show the presence of any shunts, and the arterial oxygen saturation did not decrease during exercise.

TABLE IV. ANGIOCARDIOGRAPHIC FINDINGS IN EBSTEIN'S DISEASE

CASE	RIGHT ATRIUM	RIGHT VENTRICLE	EMPTYING OF RIGHT ATRIUM AND VENTRICLE	FILLING OF PULMONARY ARTERY	FILLING OF THE AORTA ABNORMALLY EARLY	SPECIAL FINDINGS
Reynolds, 1950	Grossly enlarged	?	Delayed	Delayed and poor		
Baker et al., 1950, Case 1			Delayed	Poor		Interatrial septal defect visible
Baker et al., 1950, Case 2	Large	Late filling	Delayed	Poor	+	Interatrial septal defect visible
Engle et al., 1950, Case 2	Large	Thin-walled	Delayed	Poor	+	Interatrial septal defect visible
Soloff et al., 1951	Huge	Separated by a narrow band into a functioning and auricularized part	?	Not visible		Interatrial septal defect visible
Goodwin et al., 1953, Case 1	Enlarged	?	Delayed	Not visible		
Goodwin et al., 1953, Case 2	Enlarged	Tricuspid notch displaced to the left	Delayed	Poor		Interatrial septal defect visible
Present Case 1	Huge	Thin-walled and late filling	Delayed	Delayed		
Present Case 2	Huge	Late filling	Delayed	Delayed and poor	+	Interatrial septal defect visible

Angiocardiography has been performed in seven cases published earlier (Table IV). In six of these cases information is given of a considerable enlargement of the right atrium. In six cases delayed emptying of the right atrium and ventricle was seen, and all cases showed delayed and poor filling of the pulmonary artery, or no filling at all. In five cases an interatrial septal defect was visualized.

Angiocardiography was performed in two of our cases (Table IV). An enormous enlargement of the right atrium was seen, and there was delayed emptying of the right atrium and ventricle and delayed filling of the pulmonary artery. An associated interatrial septal defect was visible in one of the cases. In Case 1 the right ventricular wall apparently was thinner than normally found.*

DISCUSSION

Until recent years the diagnosis of Ebstein's anomaly has been maintained to be impossible during life, and the early reports are on autopsy cases. During recent years reports have been given of cases, where the diagnosis has been established during life by means of cardiac catheterization and angiocardiography. Such a diagnosis cannot be claimed to be absolutely well founded without autopsy control.

The clinicoroentgenologic picture can suggest the diagnosis, (vide infra) but we consider angiocardiography, and particularly cardiac catheterization, diagnostically essential.

The diagnosis of Ebstein's anomaly is based on the following criteria:

1. Signs of pulmonic stenosis on roentgenographic examination (faint hilar vascular markings) or angiocardiography (delayed emptying of the right side of the heart and poor filling of the pulmonary artery).
2. Exclusion of pulmonic stenosis by cardiac catheterization.
3. Evidence of enlargement of the right atrium with distal displacement of the atrioventricular valve during catheterization or by angiocardiography.

Confirmatory diagnostic features are, if present:

4. The presence of an interatrial septal defect with veno-arterial shunt in the absence of pulmonic stenosis.
5. Ventricular pulsations in the right ventricular conus part of the left heart border only (kymography), indicating a diminished functioning right ventricle.
6. Right bundle branch block in cases with or without interatrial septal defect.

According to these criteria we have found six cases of Ebstein's anomaly among about 700 catheterized cases of congenital heart disease. Thus the anomaly is rare, particularly regarding the relatively good prognosis.

The previous exposition (Tables I and II) shows a rather uniform but uncharacteristic clinical picture. Generally some degree of dyspnea is the only symptom. On physical examination cyanosis is usually found and always attributable to an interatrial septal defect with veno-arterial shunt. Usually the physical and mental development is normal. At auscultation most cases reveal a systolic murmur, which frequently is rough and loud with maximal intensity

*Since the preparation of this manuscript we have catheterized two additional cases of Ebstein's anomaly, one in Århus and one in Copenhagen.

in the mid-or lower precordium. Many of the cases show an additional diastolic murmur, usually in the lower precordium only, and in about one-half of the cases a gallop rhythm is audible at the left sternal border.

Electrocardiography with a single exception has the patterns of right bundle branch block (Fig. 1). Other common findings are enlarged P waves and prolonged atrioventricular conduction, while T-wave changes are rare.

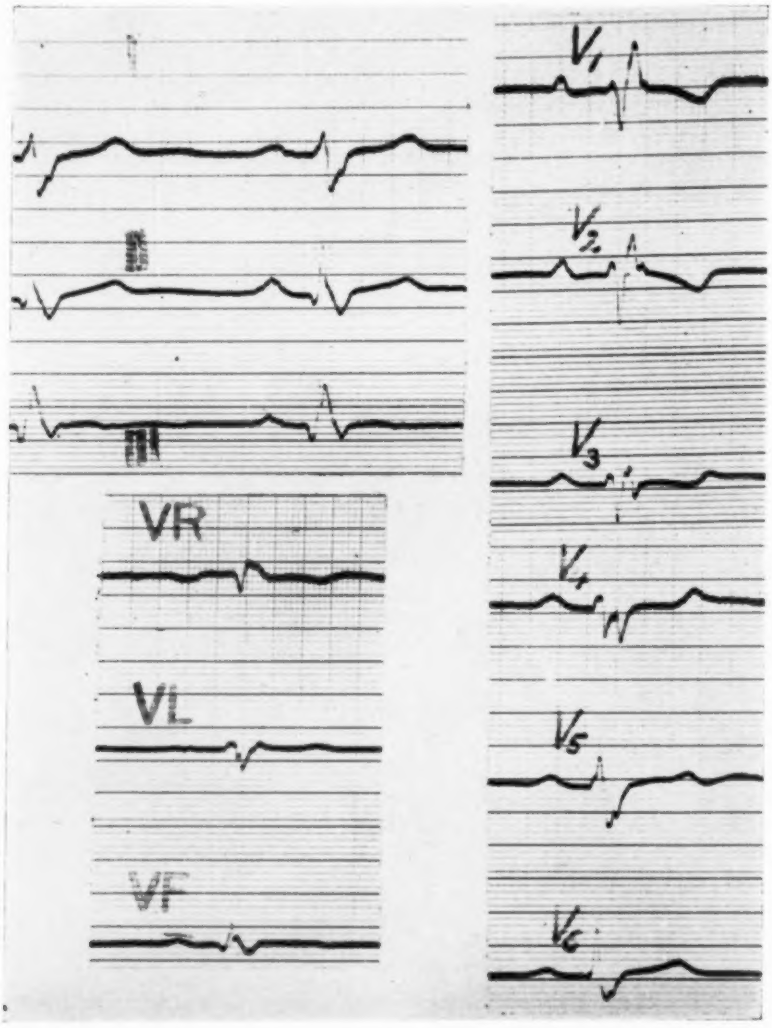

Fig. 1.—Electrocardiogram in Case 3, showing right bundle branch block with typical precordial patterns.

The most characteristic roentgenographic findings are: enlargement of the heart and one long convexity and "elevation" of the left cardiac border (identical with van Lingen and associates' "square-shaped heart".[8] Typical examples are shown in Figs. 2 and 3. In addition four of our cases at kymography showed ventricular pulsation only in the very conus part, and atrial waves in the lower part of the left heart border in the anteroposterior view (Fig. 4).

A. B. C.

Fig. 2.—Roentgenograms of Case 1. A, Right anterior oblique position; B, Anteroposterior view; C, Left anterior oblique position.

Fig. 3.—Roentgenogram of Case 2. Anteroposterior view.

Fig. 4.—Kymogram of Case 4.

Obviously the clinicoroentgenologic picture mentioned simplifies the differential diagnostic problems. An isolated interatrial septal defect or a large interventricular septal defect are excluded, as the hilar vascular markings are normal or decreased. The cardiac enlargement excludes a small interventricular septal defect. In mitral valvular disease which might be taken into consideration in cases with a history of rheumatic fever and predominantly apical murmurs, enlargement of the left atrium and increased vascularization of the lung fields would be expected.

The clinicoroentgenologic picture, however, can be identical with that of certain cases of pulmonic stenosis. A Steno-Fallot type only occasionally shows gross enlargement of the heart, and the shape of the heart in most cases is quite different from that in Ebstein's anomaly. However, noncyanotic cases of Ebstein's anomaly can be similar to cases of isolated pulmonic stenosis and cyanotic cases similar to Morgagni's syndrome.

As shown by Goodwin and associates[7] even angiocardiography may fail in establishing this differential diagnosis. An interatrial septal defect may be visualized by angiocardiography. In addition to this, Morgagni's syndrome as well as Ebstein's anomaly shows enlargement of the right side of the heart, and a delayed emptying of the right side of the heart is always seen. If a pulmonic stenosis is not directly seen and if special structures in the wall of the right atrium, indicating the rudiments of the normal atrioventricular valve (described by Soloff[11]), cannot be visualized or relied upon, angiocardiography cannot give the differential diagnosis. Cardiac catheterization, therefore, is the determining method of examination.

Cardiac catheterization makes possible the estimation of the size of the right atrium, as the distal displacement of the tricuspid valve can be seen by combined fluoroscopy and observation of the pressures. The most important catheterization finding, however, is the normal right ventricular pressure, which beyond doubt excludes pulmonic stenosis. In addition the presence of an interatrial septal defect in some cases can be verified by direct catheterization. The presence of a veno-arterial shunt can be determined by measuring the arterial oxygen saturation at rest and during exercise (oximetry).

On theoretical considerations[6] cardiac catheterization has been suggested as dangerous in cases of Ebstein's disease. The catheterization of the pulmonary artery, or at least of the right ventricle, is essential for the diagnosis. Because of the difficulties in the performance of this in Ebstein's disease, the procedure may be of long duration. In spite of this no complications have been seen in our cases.

In considering the anatomy of Ebstein's disease one should expect tricuspid regurgitation to occur in some cases. In a few cases in the literature an enlargement of the liver has been recorded, in one case with pulsations.[12] Venous congestion is mentioned in only one patient, dying from congestive failure. The clinical signs of tricuspid insufficiency are very unreliable. One of our cases (Case 5) had hepatic pulsation, but the atrial pressure curve did not agree with the presence of tricuspid insufficiency. Marked pulsation of the veins of the neck

was observed in only one of our cases (Case 3). This was the only case with signs of tricuspid regurgitation in the pressure tracing from the right atrium (Fig. 5).

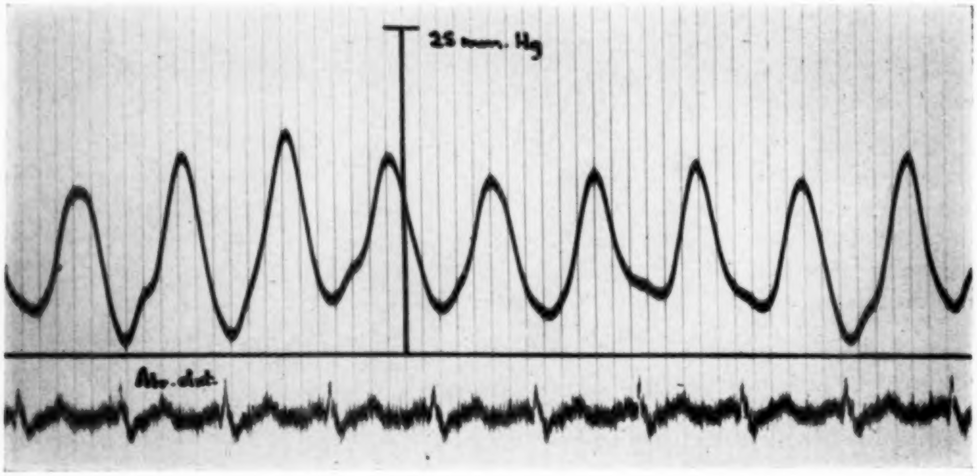

Fig. 5.—Right atrial pressure tracing from Case 4, indicating the presence of insufficiency of the tricuspid valve.

SUMMARY

A review of the literature, concerning Ebstein's anomaly of the heart, is given, and in addition six cases of our own are reported.

The symptoms are not characteristic. The signs are a rough and often loud systolic murmur, frequently a diastolic murmur in the middle or the lower part of the precordium, and in about one-half of the cases a diastolic gallop rhythm. The electrocardiograms generally show right bundle branch block, occasionally large P waves and prolonged atrioventricular conduction. Roentgenographic examination shows a big heart, frequently with a characteristic convexity and "elevation" of the left cardiac border, normal or faint hilar vascular markings, and normal peripheral lung fields. Kymography can show decreased pulsations with ventricular waves only on the middle of the left cardiac border.

Angiocardiography gives a picture with delayed emptying of a large right atrium and right ventricle, more often seen in pulmonic stenosis without interventricular septal defect. Because normal pressure is found in the right ventricle, catheterization of the heart most frequently is essential for establishing the differential diagnosis to pure pulmonic stenosis and Morgagni's syndrome. Catheterization of the heart can furthermore show the displacement of the tricuspid valve and the presence of an interatrial septal defect.

CASE REPORTS

Case 1.—(J.R.A.) The patient was a girl, 10 years of age. No cases of heart disease were reported in the family. The mother had been healthy during the pregnancy.

In early childhood the patient had scarlet fever without complications. At 8 years of age she was hospitalized because of chorea. For short periods this disease had recurred. While in hospital choreatic movements were only observed once.

She had always had tendency to dyspnea, associated with cyanosis and palpitation on exertion. Squatting had never been observed, and there had been no attacks of precordial pain or fainting. There was some cough and expectoration.

Physical examination: Height, 137 cm.; weight, 29.8 kg. She was normally developed and her intelligence corresponded to her age. Moderate cyanosis of the skin and mucous membranes was noted. There was no dyspnea at rest.

The lungs were normal on examination.

The cardiac rhythm was regular. Slight bulging of the precordium was observed. The apex beat was palpable in the fifth left intercostal space, 2 cm. lateral to the mid-clavicular line. A rough systolic murmur of moderate intensity, and a faint, rough, end-diastolic murmur with maximum at the apex were heard. P_2 was louder than A_2. A third heart sound was heard at the apex.

The liver was not palpable. No pulsation of the veins of the neck was found. There was slight clubbing of the fingers. The femoral pulse was normal.

Laboratory findings: Blood pressure in the arm was 90/60 mm. Hg. The sedimentation rate was 2 mm. The hemoglobin, 115 per cent, and the red blood cell count, 4.78 million; hematocrit, 44; Wassermann test, negative; the antistreptolysin titer, 250. The urine contained no abnormal constituents.

Electrocardiograms: An incomplete right bundle branch block was found. The QRS duration, 0.10 sec.; QRS, M-shaped and notched in V_1 and notched but not quite typical in V_2 (rS), but there was typical broad S in V_5. The QRS axis was between +120 and +150°. The Wilson position was vertical. T axis between 0 and 30°. P_2 was high and PQ slightly prolonged (0.20 sec.). No arrhythmias.

Roentgen examination: Cardiac index, 0.67; heart volume, 720 ml. The right atrium was considered enlarged in the anteroposterior view and in the right anterior oblique position. In the left anterior oblique position there was considerable bulging of the cardiac silhouette both anteriorly and posteriorly. The left atrium was considered of normal size. In the anteroposterior view the left cardiac border was convex and elevated. The vascularization of the lungs was normal or slightly decreased, the hilar vascular markings were faint.

Kymography: Ventricular pulsation was seen only in the middle of the left cardiac border, the lower part of which showed atrial pulsations. The pulmonary artery was only slightly pulsating.

Cardiac catheterization: The catheter was introduced into a huge right atrium. Ventricular pressure tracings were obtainable only in the conus part of the heart. The pressure in the pulmonary artery was 14/8, in the right ventricle 18/2, and in the right atrium 7/2. A small arteriovenous shunt was found to the right atrium. The arterial oxygen saturation was 87 per cent, as evidence of a moderate right-to-left shunt through the interatrial septal defect.

The arterial oxygen saturation was seen to fall from 87 per cent to 80 per cent during exercise (270 kg. M./min.).

Angiocardiography: An enormous right atrium was visualized, and there was delayed filling of the thin-walled right ventricle. The contour of the right chambers was thought to show the remnant of the normal tricuspid valve.

CASE 2.—(Y.E.J.) This patient was a girl, 7 years of age. No cardiac diseases were reported in the family. The delivery was uncomplicated. Cyanosis was observed shortly after birth. When 4 days old she had a severe attack of dyspnea and cyanosis, but since then no critical situations had occurred. She developed normally during childhood. The cyanosis increased gradually in intensity and was accentuated and associated with dyspnea on exertion. One month before admission to the hospital she had a short period of unconsciousness, lasting half a minute, after staying in the cold. During recent years the dyspnea had been progressive.

Physical examination: Physically, she was normally developed. Slight cyanosis but no dyspnea was observed at rest. There was heavy pulsation of the precordium and a systolic thrill was palpable in the middle of the precordium. The apex beat was of maximal intensity in the left anterior axillary line. A harsh, strong systolic murmur and a weak end-diastolic murmur were audible with their maximum at the apex. A third heart sound was heard at the apex. The second pulmonic sound was louder than the second aortic sound. The rhythm was regular. The lungs were free of abnormality on examination. The liver was not palpable, and there was no pulsation of the veins of the neck. There was clubbing of the fingers.

Laboratory findings: The blood pressure in the arm was 90/60 mm. Hg. The sedimentation rate, 1 mm.; hemoglobin, 130 per cent; red blood cell count, 5.80 million; Wassermann test, negative. No abnormal constituents were found in the urine.

Electrocardiograms: Incomplete right bundle branch block, with typical precordial leads. QRS interval, 0.10 sec.; the QRS axis about +150°. Wilson position, indeterminate. T axis between 0 and 30°. P_1 and particularly P_2 were high but not abnormally broad. PQ slightly prolonged, heart frequency, 90 to 100. No arrhythmias.

Roentgenographic examination: Cardio-thoracic index, 0.74; heart volume, 850 ml. Moderate bulging of the second and pronounced bulging of the third left arch, forming one big elevated convexity.

The hilar vascular markings and the peripheral lung fields were of decreased density. In the left anterior oblique position the heart silhouette was bulging both anteriorly and posteriorly. The right atrium was considered much enlarged. The left atrium was normal. The aortic arch was narrow. The pulsations of the pulmonary artery were normal. In kymography only the mid-portion of the left heart border showed ventricular waves.

Cardiac catheterization: The catheter was seen to curl up in a huge right atrium. The pressure in the pulmonary artery was 16/4, in the right ventricle 27/2. The pressure in the right atrium was 8/2. The arterial oxygen saturation was 89 per cent as evidence of a small right-to-left shunt. No evidence was found of any left-to-right shunt.

The arterial oxygen saturation decreased from 89 to 84 per cent during exercise (270 kg.M./min.) shown by oximetry.

Angiocardiography: A huge right atrium was opacified with delayed emptying of dye into the right ventricle. Only very weak and late filling of the pulmonary artery was seen. The left side of the heart was seen to be filled from the right atrium through an interatrial septal defect.

CASE 3.—(A.L.) The patient was a 17-year-old male. No cardiac diseases were reported in the family. He had always been in good health, the heart disease excepted. Since early childhood he had cyanosis of the skin and tendency to dyspnea and palpitations on exertion, such as bicycling and climbing stairs. At school he was able to take part in gymnastics, but not in ball games, though at the time of admission to this hospital he was able to bicycle 16 km. to work every day. He had never had any thoracic pains, coughing, or fainting; and edema had never been observed. The disease had been unprogressive.

Physical examination: Height, 166 cm.; weight, 67.1 kg. There was pronounced cyanosis of the skin and mucous membranes and injection of the sclerae. The skin of the face was acnoid with phlebectases.

Examination of the lungs gave normal findings. There was no thrill or bulging of the precordium. The apex beat was palpable in the fifth left intercostal space, 2 cm. lateral to the midclavicular line. A rough, loud systolic murmur was heard over the whole of the precordium with its maximum in the third to fourth left intercostal space at the sternum. A distinct third heart sound was heard in the middle of the precordium.

The liver was not palpable, and there was marked pulsation of the veins of the neck. Pronounced clubbing of the fingers was observed. No edemas were present.

Laboratory findings: The blood pressure in the arm was 110/75 mm. Hg; sedimentation rate, 0; hemoglobin, 159 per cent; the red blood cell count, 6.72 million; hematocrit, 66; basal metabolism, 102 per cent.

Electrocardiograms: Right bundle branch block with typical precordial leads; QRS interval, 0.12 sec. QRS axis between +90° and +150°. Wilson position, semivertical. T axis about +30°.

P_2 and particularly P_1, high but not abnormally broad. P-Q, normal. Heart frequency, 75. No cardiac arrhythmias.

Roentgen examination: Cardio-thoracic index, 0.50; heart volume, 985 ml. Heart shape normal in the anteroposterior view. Slightly decreased hilar vascular markings, normal density of the peripheral lung fields. The heart shape was normal in the oblique views, except for slight bulging anteriorly in the left anterior oblique position.

Kymography: Only the mid-portion of the left heart border showed ventricular pulsation. Pulsation of the main pulmonary artery was decreased.

Cardiac catheterization: The catheter after introduction into the conus part of the right ventricle passed in a big bow back into the atrium, and it was thus not possible to catheterize the pulmonary artery in spite of numerous attempts. Ventricular pressure tracings were obtained only in the conus part of what was thought to be the right ventricle. The catheter was passed through an interatrial septal defect into the left atrium and ventricle. The pressure in the right ventricle was 25/1 mm. Hg. The atrial pressure tracing showed a pronounced V wave, 8/1 mm. Hg. The arterial oxygen saturation was decreased as evidence of a right-to-left shunt through the septal defect. No evidence was found of a left-to-right shunt.

The arterial oxygen saturation decreased from 89 per cent to 75 per cent during exercise (270 kg.M./min.).

CASE 4.—(K.S.) The patient was a 26-year-old man. The father was suffering from heart disease of unknown character. Until 18 years of age when dyspnea developed on exertion, the patient had been healthy. There had been no symptoms of heart disease until then, and he was able to take part in gymnastics while at school. From the beginning of the symptoms until the time of hospitalization the dyspnea had been gradually increasing and associated with palpitations, and he was now able to run only 100 meters at moderate speed. Lately, he had attacks of precordial pains during exercise, but cyanosis had never been observed.

Physical examination: Height, 174 cm.; weight, 74.6 kg. No dyspnea or cyanosis were observed at rest. Examination of the lungs revealed no abnormalities.

There was heavy pulsation, but no bulging of the precordium. The apex beat was palpable in the fifth left intercostal space, 1 to 2 cm. lateral to the mid-clavicular line. A rough and faint systolic murmur and a very faint diastolic murmur were heard with maximal intensity at the apex. The second pulmonic sound was louder than the second aortic sound, but not accentuated. The cardiac rhythm was regular.

The liver was not palpable. There was marked pulsation of the veins of the neck. No clubbing of the fingers or toes was observed. No edema was present.

Laboratory findings: The blood pressure in the arm was 120/65 mm. Hg. The sedimentation rate, 2; the hemoglobin, 105 per cent; Wassermann test, negative; antistreptolysin titer, 80. No abnormal constituents were found in the urine.

Electrocardiograms: Right bundle branch block; mean axis of QRS, 120°; mean axis of T, 30°; duration of QRS, 0.14 sec. P_1 and P_2 somewhat broad (0.12 sec.) but of normal amplitude; P-Q normal. The heart was in a vertical position according to Wilson's criteria.

Roentgenographic examination: Cardio-thoracic index, 0.54; heart volume, 1,500 ml. In the anteroposterior view a slight prominence of the pulmonary arch was continuous with a bulging third left arch, resulting in convexity and elevation of the whole left cardiac border. The heart was slightly enlarged to the right. The heart was broad in the left anterior oblique position, the left atrium estimated to be normal and the right to be slightly enlarged. The hilar vascular markings were of decreased density, and the peripheral lung fields were normal.

In *kymography* the main stem of the pulmonary artery only showed small pulsations, and the lowest part of the left cardiac border showed atrial waves. So the characteristic feature of the kymogram was that ventricular waves were only seen in the mid-portion of the left cardiac border.

Cardiac catheterization: An enormous dilatation of the right atrium was found. Ventricular pressure tracings were obtained only in the conus part of the heart. The pressure in the pulmonary artery was 17/10 mm. Hg, that of the right ventricle was 22/4 mm. Hg. The atrial pressure was 15/3 mm. Hg, and the tracing showed a small a-wave and a large V-wave. No evidence of shunts was found (For details see Fig. 5).

Oximetry showed a decrease of arterial oxygen saturation from 93 to 91 per cent during exercise (540 kg.M./min.).

CASE 5.—(O.D.J.) The patient was a 22-year-old man. The family history was noncontributory. Except for the heart disease he had suffered from no serious diseases during childhood. As far back as he remembered he had dyspnea on exertion. He had been able to walk as far as his contemporaries, but in ball games he had been handicapped because of dyspnea and palpitations. He was able to climb stairs without difficulty. The heart disease was diagnosed at 20 years of age. Since then dyspnea and palpitations had been of increasing intensity and in the last months before admission to the hospital he had attacks of precordial pain and dizziness, lasting a few seconds. Fainting had never occurred. Because of the cardiac symptoms he had to give up his work as a radio technician. There was no history of edema or acute attacks of dyspnea, or cyanosis.

Physical examination: The patient was a normally developed man. Height, 165 cm.; weight, 60.3 kg. No cyanosis or dyspnea was observed at rest. The lungs were normal on examination. There was no bulging of the precordium, or palpable thrill. The apex beat was palpable in the fifth left intercostal space in the mid-clavicular line. A rough, moderate systolic murmur was heard with maximal intensity at the apex. The second pulmonic sound and the second aortic sound were of equal intensity. The cardiac rhythm was regular.

Pulsation of the liver was observed, but no pulsation of the veins of the neck. There was no clubbing of the fingers or toes. No edema was present.

Laboratory findings: The blood pressure in the arm was 110/60 mm. Hg. The sedimentation rate, 5 mm.; hemoglobin, 106 per cent; red blood cell count, 4.90 million; and the hematocrit, 46. Wassermann test, negative; basal metabolic rate, 101 per cent. The urine was found normal.

Electrocardiograms: Right bundle branch block with typical precordial leads. QRS interval, 0.12 sec.; QRS axis, between $+120°$ and $+150°$. Wilson position, semihorizontal; T axis between $0°$ and $+30°$. P_2 slightly enlarged; PQ in the upper limit of normal (0.22 sec.); heart frequency, 60. No arrhythmias.

Roentgenographic examination: Cardio-thoracic index, 0.62; heart volume, 1,340 ml. Slight bulging of the second and the third left arch, forming one big convexity. The hilar vascular markings were decreased in density. The peripheral lung fields were normal. The right atrium was considered much enlarged, and the heart was broad in the left anterior oblique position.

Kymography: Ventricular pulsations of the whole left border. Normal pulsation of the pulmonary artery.

Cardiac catheterization: The right atrium was found considerably enlarged. It was difficult to catheterize the pulmonary artery as the catheter, when apparently in the outflow tract of the right ventricle, curled back into the atrium. Low pressures were found in the pulmonary artery and right ventricle. When the catheter was withdrawn from the right ventricle, atrial pressure tracings were obtained abnormally early. There was found no evidence of shunt. The arterial oxygen saturation was normal.

The arterial oxygen saturation showed a decrease from 96 to 92 per cent during exercise (675 kg.M./min.).

CASE 6.—(B.K.A.) The patient was a man 21 years of age. No cases of heart disease were found in the family. He had suffered from no serious diseases during childhood. He had always had a tendency for dyspnea on exertion. While at school he was not able to take part in gymnastics. As far back as he remembered, he had cyanosis, which was accentuated during exercise. Squatting had never been observed, and it was the patient's impression, that his symptoms had decreased during later years. He was able to climb stairs to the third floor, where he had to pause because of dyspnea and palpitations. After exertion he always had coughing, but no expectorating. Hemoptysis had never occurred. Two months before admission to this hospital he had pneumonia.

Physical examination: The patient was a normally nourished man. Height, 177 cm.; weight, 52.8 kg. There was no dyspnea at rest, but slight cyanosis of the skin and mucous membranes. No pulsation in the veins of the neck. The lungs were normal on examination.

There was no bulging of the precordium and no palpable thrill. The apex beat was of maximal intensity 1 cm. medial to the frontal axillary line. A weak blowing, systolic murmur was heard at the sternum in the third and fourth left intercostal spaces. No diastolic murmurs were found. In the middle of the precordium a systolic gallop rhythm and eventually a split second sound were

heard, making a quadruple rhythm. The second pulmonic sound was slightly louder than the second aortic sound. The rhythm was regular.

The liver was not palpable; no clubbing of the fingers or toes; no edema was present.

Laboratory findings: The blood pressure in the arm was 130/80 mm. Hg. The sedimentation rate, 2; hemoglobin, 115 per cent; red blood cell count, 5.55; hematocrit, 51 per cent; Wassermann test, negative; basal metabolic rate, 100 per cent. No abnormal constituents were found in the urine.

Electrocardiograms: Wolff-Parkinson-White block (left bundle branch block). QRS-axis between +30° and +60°; Wilson position, horizontal. T axis between 0° and +30°. P_1 and P_2, notched; PQ duration, 0.12 sec.; QRS duration, 0.16 sec.; rhythm normal; ventricular premature beats.

Roentgenographic examination: Cardio-thoracic index, 0.59; heart volume, 680 ml. Normal second left arch, bulging left third arch with convexity but no elevation and convexity of the whole left cardiac border. The heart was enlarged towards the right. The hilar vascular markings were faint. The peripheral lung fields were normal. Bulging of the anterior outline in the left anterior oblique position. The upper part of the third left arch showed atrial pulsations, and above this, ventricular waves were visible in a small area.

Cardiac catheterization: The right atrium was found considerably enlarged, and the tricuspid valves were found displaced towards the conus part of the right ventricle. Low pressures were found in the pulmonary artery and the right ventricle and atrium. The oxygen analyses indicated the presence of a left-to-right shunt to the right atrium, but it was not technically possible to catheterize a defect. The arterial oxygen saturation was 90 per cent during rest, with a decrease to 75 per cent during exercise (400 kg.M./min. for 5 minutes).

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Clinical Reports

CONGENITAL HEART DISEASE AND ACUTE MYOCARDIAL INFARCTION

HARRY VESELL, M.D.

NEW YORK, N. Y.

IN A recent study,[1] the general incidence of congenital heart disease was estimated at 0.14 to 0.16 per 1,000. In this same survey, in an autopsy series, covering the boundary of Birmingham, England, however, the incidence was found to be 3.2 per 1,000 total births. Other estimates of incidence[2-5] have fallen between these two. Ventricular septal defect is usually considered the first or second most frequent type of congenital heart disease.[6,7] More often, other cardiac lesions are also present. In Abbott's series of 1,000 cases,[7] 207 of 257 were such, and only fifty were pure ventricular septal defects. Of the fifty, with this single cardiac lesion, the maximum age was 49 years; the average only 14.5 years. Abbott considered the typical small defect, just anterior to pars membranacea, as not itself hampering the work of the heart, but as having a serious clinical import in the frequent incidence of bacterial endocarditis about the margins of the defect, or at the point of impact of the blood stream on the opposite wall of the right ventricle.[8] In the series of Gelfman and Levine,[5] bacterial endocarditis occurred in 57 per cent of those over 2 years of age, with Rogers disease. Ventricular septal defect was the lesion in twenty-six of the Mayo Clinic's 212 specimens with major cardiovascular abnormalities.[9] In the four oldest of the twenty-one patients with defects involving the membranous portion of the septum, the ages were 12, 13, 21, and 53 years. In Seltzer's cases,[10] twelve of his own and eighty from the literature, sixteen were over 30 years, six of whom were over 50 years of age. Eighteen, or twenty per cent, died of subacute bacterial endocarditis; 28 per cent of those were over one year of age. The majority succumbed to causes unrelated to the cardiac malformation, mostly noncardiac. He noted that only an occasional patient survived beyond early middle life. Thus, there would not be many living to the coronary age, so that myocardial infarction in patients with ventricular septal defects should be very uncommon or extremely rare. Indeed, no reference in the literature was found to the occurrence of myocardial infarction in patients with interventricular septal defects. The resultant effect of the two lesions on cardiac behavior is of interest, as is a comparison with the condition of acute myocardial infarction with perforation of the interventricular septum.

From the Department of Medicine and Cardiographic Laboratory, Beth Israel Hospital, New York City.

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CASE REPORT

H. L., a 34-year-old white man, was first seen at our private office, for a cardiac examination, in 1931, when he was 13 years of age. His mother stated that he was not a blue baby at birth, but that a heart murmur was heard early in infancy, and since then, he was thought to have congenital heart disease by doctors in attendance. In infancy and childhood, he had had pertussis, diphtheria, measles, varicella, mumps and the "grippe." He had played games with other boys, but found that he tired more easily. At 13 years, he weighed 120 pounds, appeared well developed and well nourished. He was not cyanotic or dyspneic. The examination of the heart was recorded as indicating the apex impulse felt in the fifth intercostal space, 9.5 cm. from the midclavicular line; the right border percussed at the right sternal margin. A loud, rasping systolic murmur was heard over the entire precordium, loudest at the third and fourth intercostal spaces, just left of the sternum. The blood pressure was 124/64 mm. Hg. On fluoroscopy, the heart appeared slightly enlarged and globular. An electrocardiogram, taken in 1931, was noted as normal, but the tracing was not located. In 1933 he was seen again because of an upper respiratory infection. At this time, he weighed 140 pounds. A systolic thrill was palpated just to the left of the sternum at the level of the nipple, where the loud, long rasping systolic murmur was noted as being best heard. The murmur was transmitted in all directions, best up the sternum to the suprasternal notch, next best to the left, but also heard faintly in the back at the angle of the scapula. A_2 was louder than P_2; the rate was 74 and regular; the blood pressure was 130/80 mm. Hg. A sketch was made of the cardiac silhouette on fluoroscopy. In the anterior position, the heart appeared slightly enlarged to the left and globular. The cardiac index was about 50 per cent. There were increased systolic pulsations of the left and right ventricular borders. In the right anterior oblique position, the anterior border, with both upper and lower segments, was prominent, but there was no increase in prominence of the posterior, left atrial border. In the left anterior oblique, there was increased extension of the posterior left ventricular border, and slightly increased extension of the anterior right ventricular border. He was next examined in 1936, when 18 years of age, and similar cardiac findings were noted. He weighed 155 pounds. In 1946, he was examined again. He had been feeling well and working regularly. He indulged in mild athletics, playing ping-pong and rowing without undue discomfort, but did feel faint and dizzy in more strenuous games, and on a few occasions even experienced syncope. At this examination, the above cardiac findings were again corroborated. The thrill and rasping systolic murmur were noted. Blood pressure was 134/90 mm. Hg. It was also observed that there were no pulsations in the interscapular region and that the femoral arterial pulses were normal. The diagnosis of interventricular septal defect was recorded. He was seen briefly, in 1947 and in 1948, for minor prostatitis and abdominal complaints; some tenderness over the appendix area was noted. The blood pressure was 130/90 mm. Hg; after exercise, 10 body bends, 144/70 mm. Hg, and after 10 more bends, 140/70 mm. Hg. This was a response to exercise, seen in other patients with interventricular defects, slight elevation of the systolic and some depression of the diastolic blood pressure.[11] The systolic murmur was loudest at the fourth left intercostal space, about 4 cm. from the mid-sternum. In 1949, a premarital examination was made, and the blood Wassermann was reported negative. He was next seen on May 8, 1952, for an examination prior to applying for insurance. The murmur was noted as loudest, Grade 3 to 4, (maximum 6) at Roger's point. The cardiac silhouette on fluoroscopy was sketched as globular, with the right and left borders out 1 plus. Pulsations of the ventricular borders were increased in amplitude. An electrocardiogram (Fig. 1) revealed left-axis deviation with angle alpha $-40°$; P waves were normal; P-R, 0.16 sec., QRS, 0.11 sec., with a 4 mm. 0.04 sec. S in Lead I, a 1.2 mm. r′ in V_1; the transitional precordial zone between V_3 and V_4; R was 10 mm. in aV_L; S was 5 mm. in aV_F, preceded by a 1 mm. R wave; a horizontal (electrical) positioned heart. The wide QRS, S_1, and r′ in V_1 suggested the presence of incomplete right bundle branch block. There was no history of cough, hemoptysis, dyspnea, orthopnea, ankle edema, cyanosis, hypertension, diabetes, rheumatic fever, or chorea.

On Feb. 16, 1953, in the course of his regular daily work, walking leisurely, he was suddenly seized with pain in the chest, a heavy compressive feeling in the mid-substernal region.

5/8/52
2/17/53
2/19/53
3/6/53
4/3/53

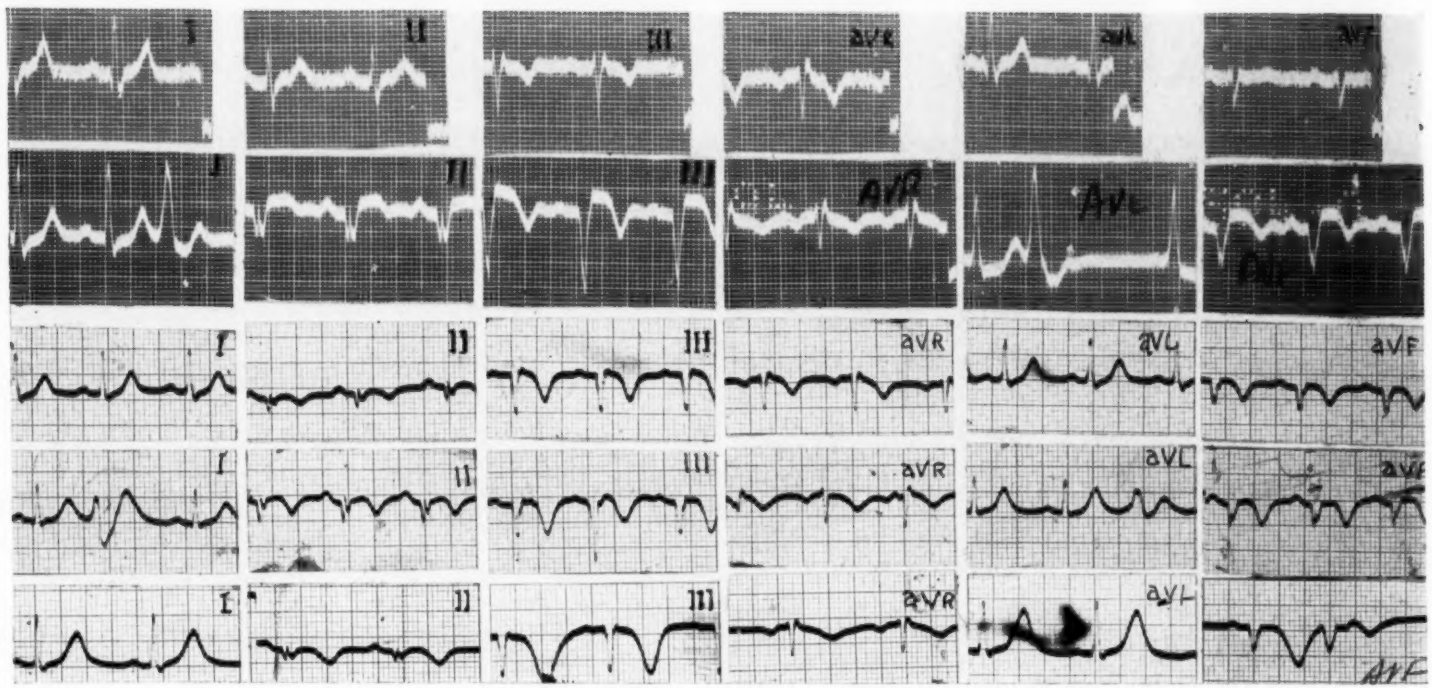

Fig. 1A.—Standard and augmented unipolar limb lead electrocardiograms: 5/8/52, before attack: 2/17/53, on second day of attack, deep Q and elevated RS-T in Leads II, III, and aV_F, as in acute posterior wall myocardial infarction. On 2/19, 3/6, and 4/3/53 serial changes, see text. Electrocardiogram of 2/20/53 was similar to that of 2/19/53 and is omitted.

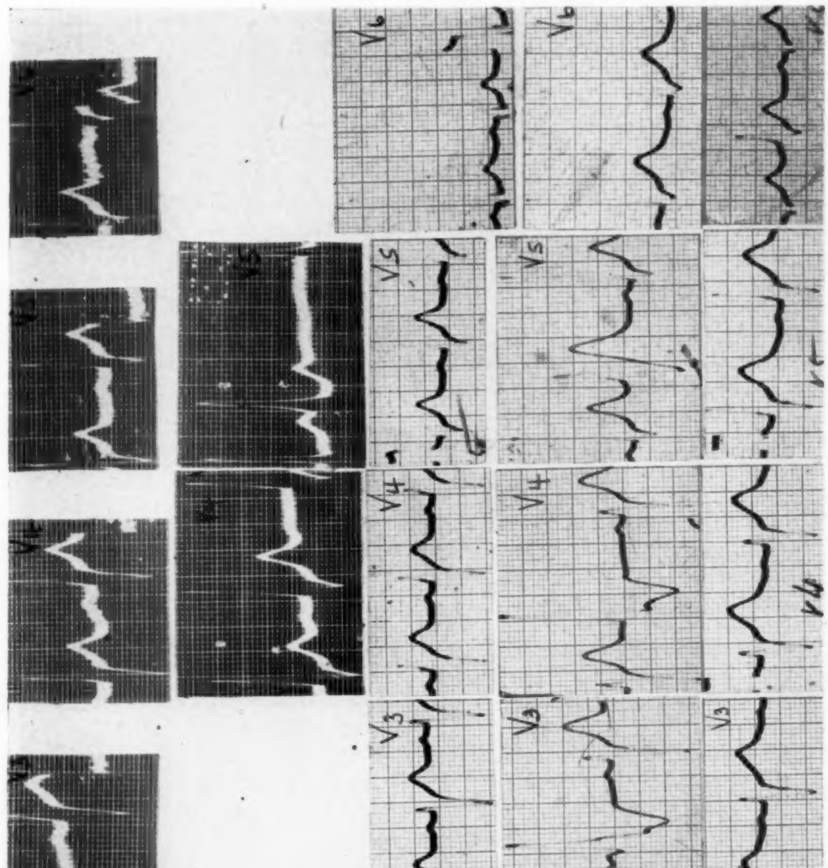

Fig. 1*B*.—Unipolar precordial leads.

He perspired profusely. He was taken by ambulance to the Queens General Hospital, where a diagnosis of acute myocardial infarction was made, corroborated by the electrocardiographic findings. The pain persisted until relieved by a hypodermic, given when he arrived at the hospital. For several hours, only mild chest discomfort remained. On the third day, he was transferred to the Beth Israel Hospital. At this time, he appeared in no distress, lying quietly in bed, with no pain, dyspnea, or cyanosis. His temperature was 101° F. The eyes presented some exophthalmus; the left pupil was larger than the right, and slightly irregular; both reacted to light and accommodation. An injury in childhood was said to account for the pupillary changes. The fundi were considered normal. The neck veins were not visibly distended. There was no thyroid enlargement and no adenopathy. No deformity of the chest was observed. The point of maximal apical impulse was in the fifth left intercostal space, 2 cm. lateral to the midclavicular line. The cardiac rate was 104 and regular. The systolic thrill and murmur were noted; the murmur, recorded as Grade 4, was heard over the entire precordium, but loudest at the fourth left intercostal space, at the junction with the sternum. In this region, it replaced, or largely masked, the first heart sound, a quality noted in cases of interventricular septal defect, by ourselves and others.[12,13] It was transmitted to the right as well as to the left, also to the neck and back. The second pulmonic sound was louder than the second aortic, and slightly accentuated. The blood pressure was 110/70 mm. Hg. Liver, spleen, and kidneys were not palpable. The genitalia appeared normal. There was no edema of the extremities. Normal arterial pulsations were felt in the arms and legs. No sensory, motor or reflex changes were observed. The diagnosis was: congenital heart disease; interventricular septal defect; arteriosclerotic heart disease; coronary sclerosis; acute coronary occlusion with acute myocardial infarction; regular sinus rhythm; incomplete right bundle branch block. Class ii, E.[14]

Laboratory Data.—On routine examination of the urine, the specific gravity was 1.012 and 1.014; a trace of albumen was noted; 8 to 10 red blood cells per high-power field were seen. On April 12, the white blood count was 12,400, with 64 per cent polymorphonuclears, 23 per cent lymphocytes, and 3 per cent monocytes. There were twelve grams of hemoblogin per 100 c.c.; the erythrocyte sedimentation rate (Westergren) was 37 mm. in one hour. The blood cholesterol was 152 mg. per 100 c.c., 88 mg. esters. Electrocardiogram: The tracing taken on Feb. 17, 1953, (Fig. 1) revealed a prominent Q_2, Q_3 and Q_{aVF}, with RS-T elevations, and coving of the T, characteristic of that seen in acute myocardial infarction of the posterior wall.

He was placed on bed rest, a salt-poor diet, necessary sedatives, and anticoagulant therapy with Dicumarol. He remained comfortable, and the course of illness was uneventful until March 6—the eighteenth day—when he awoke in the morning with pains in the right lower quadrant of the abdomen over the region of the appendix. There was local tenderness and rebound tenderness. The white blood count rose to 19,400 with 91 per cent polymorphonuclears. The temperature was 100.4° F. The diagnosis of acute appendicitis was made and corroborated at surgical consultation. Anticoagulants were discontinued. Treatment consisted of intravenous feedings, and antibiotics, with large doses of penicillin and streptomycin, given intravenously; Aureomycin and Gantrisin were added. The abdominal distress gradually subsided over several days, and the patient again was comfortable, and the blood count normal. On March 14, because of the appearance of an increase in the number of premature ventricular contractions, he was given quinidine sulphate, 0.2 Gm., every six hours, with some decrease in the extrasystoles. On March 26, there was a recurrence of the appendicitis, with pain, tenderness, and fever of 102.6° F. This attack also subsided after several days of intravenous feedings and antibiotic therapy. On April 1, he felt well again. Ambulation was started. There was no evidence of cardiac failure. The venous pressure, in an anticubital vein, on April 4, was 90 mm., without rise on pressure in the right upper abdomen; arm-to-tongue circulation time with Decholin was 16 seconds. Electrocardiograms were taken on Feb. 19, 20, March 6 and April 3, (Fig. 1) and revealed serial changes of acute myocardial infarction, compared with the original electrocardiogram, Feb. 17, 1953, particularly in the RS-T displacement and T waves, in Leads II, III and aV_F. The electrocardiogram of April 3, 1953, had a long Q-T interval with large, wide awkward looking T waves, probably due, in large part, to quinidine, and electrolyte disturbance caused by intravenous feeding. A ballisto-

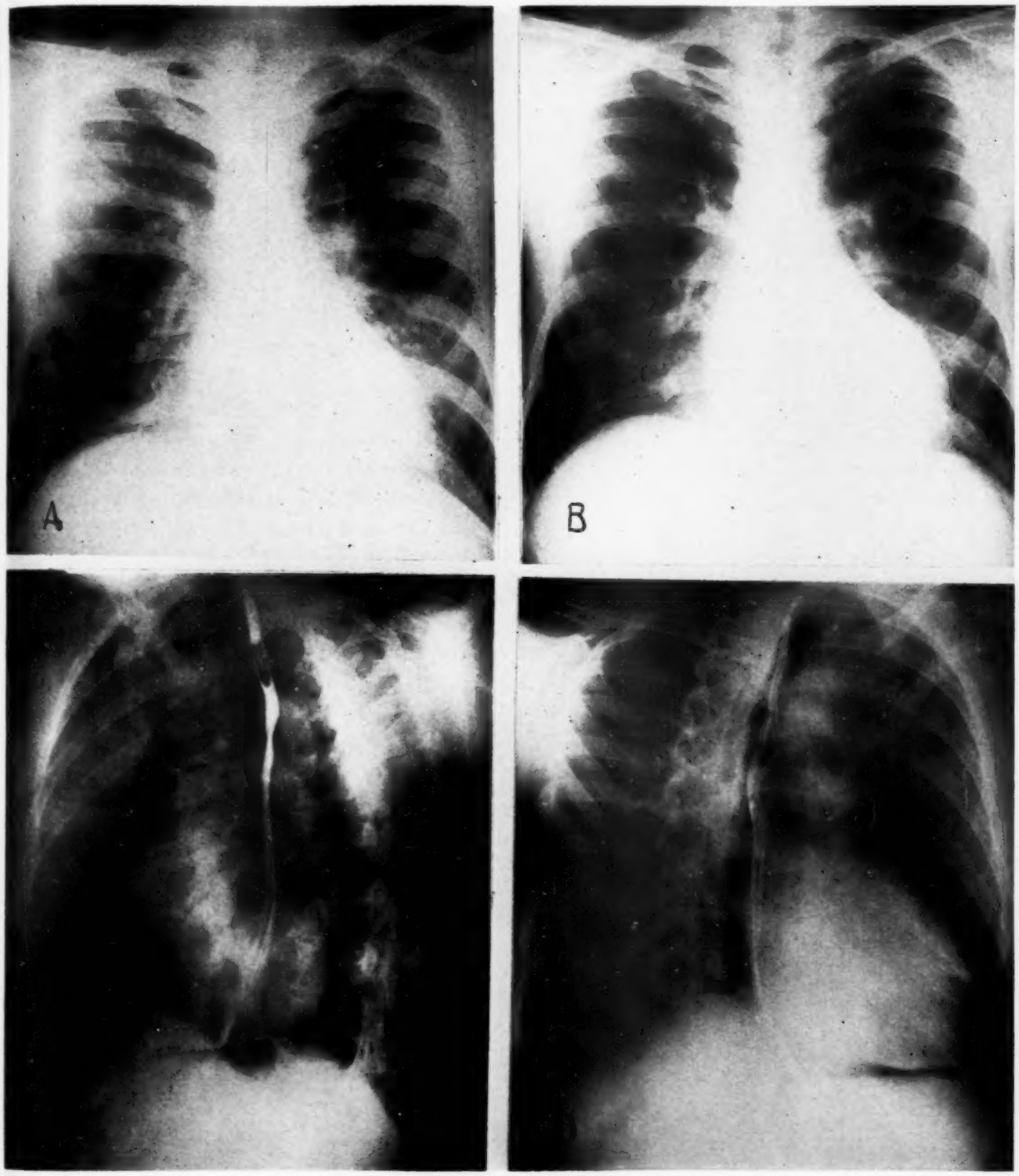

Fig. 2.—*A*, Teleroentgenogram on May 27, 1952; courtesy of Dr. Louis B. Dunn: 9 months before attack; transverse diameter of the heart 150 mm.; predicted (Hodges-Eyster) 135 mm.; normal or slightly increased hilar markings. *B*, 6/25/53—After attack; anteroposterior view, transverse diameter 156 mm. *C*, 6/25/53—Left anterior oblique view, globular shaped heart. Evidence of left ventricular enlargement. *D*, 6/25/53—Right anterior oblique view; barium in esophagus. Left atrium not definitely enlarged.

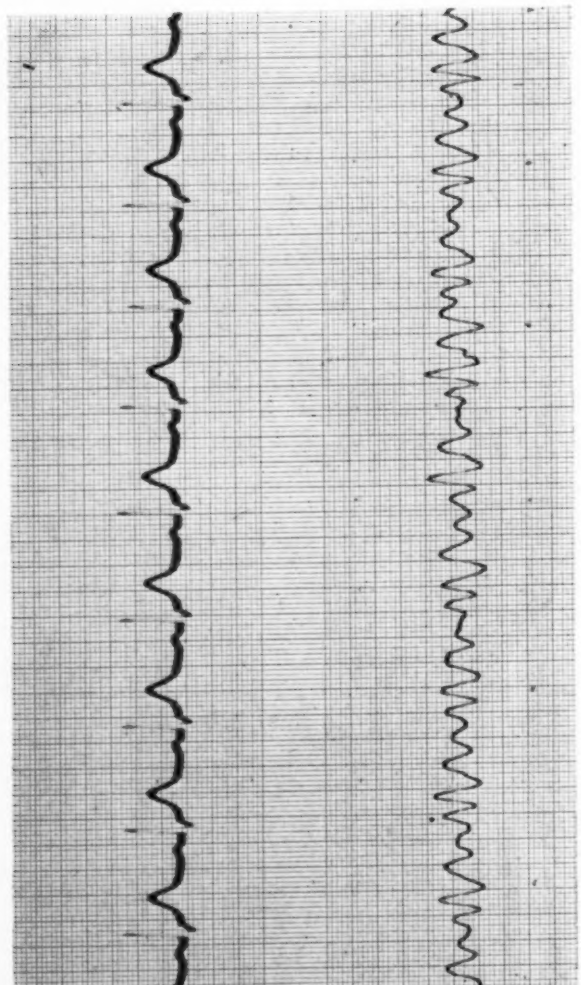

Fig. 3.—Ballistocardiogram with Lead I of electrocardiogram. See text.

cardiogram on April 6 (Fig. 3), taken simultaneously with Lead I of the electrocardiogram, revealed H, I, J, K waves of normal size and contour. Q-H was 0.09 sec., Q-I, 0.16 sec., Q-J, 0.20 sec., and Q-K, 0.30 sec. The H, I, J, K pattern was repetitive except for the premature contractions. The ballistocardiographic findings were within the limits of normal. The normal amplitude of the waves may be due to the balance between increased wave magnitude, as seen in patients with cardiac shunts and the abnormally low amplitude seen in those with coronary artery disease and myocardial infarction.

DISCUSSION

The coincidence of myocardial infarction and congenital heart disease, with the exception of the anomalies of the large vessels and coronary arteries, is rare. Benign congenital cardiac lesions with good prognosis and length of life into the fifth, sixth, and seventh decade, should yield such coincidence. A search of the literature, however, failed to reveal reports of them, except for dextrocardia.[15] Simple ventricular septal defect, in spite of the general impression of its benignity,[8,16] had an average life span in the Abbott series of only 14.5 years.[7] The rarity of its association with arteriosclerotic heart disease and acute myocardial infarction is thus explicable. No report of this combination of lesions could be found in the literature, though it most probably has occurred and not been reported, or not been recognized. In our case, the diagnosis of ventricular septal defect was established by the presence of the murmur from early infancy, the absence of a history of rheumatic fever, the typical location and character of the systolic thrill and the murmur of Roger, the latter considered pathognomonic by its author,[17] and traced by catheterization to the site of the septal defect by Cournand and his associates,[18] the slightly enlarged globular-shaped heart with increased pulsations of the left and right ventricular border,[19] and the electrocardiogram with left-axis deviation, and some disturbance of conduction.[20] The episode of acute myocardial infarction was typical in its clinical and laboratory manifestations, with characteristic evolution of serial electrocardiographic changes. This episode occurred at the age of 34 years. The comparatively mild course (excluding the appendicitis) without shock or cardiac failure is to be noted in the presence of the two important cardiac lesions. This mild course is also in contrast to the severity of the condition of acute myocardial infarction, complicated by perforation of the ventricular septum, in eighty-eight cases reported in the literature.[21,22] In addition to the different location in the septum at which the perforation takes place, usually in the lower part, the extent of the infarcted area and the amount of coronary artery disease may be substantially different in the latter type of case than in the one described in this paper. What effect, if any, the lifelong ventricular septal defect may have on the architecture, function, and disease of the coronary arteries is unknown. In our case, during the acute attack, the signs of the congenital septal defect remained without noticeable change; the thrill and murmur persisted in about the same intensity. No marked drop in blood pressure occurred. Before the attack, in May, 1952, it was 128/90 mm. Hg; during the first week of the myocardial infarction, 104/60 mm. Hg, and 110/70 mm. Hg, and on April 25, 1953, it was 114/84 mm. Hg.

The cardiac rate after the first few days stayed between 60 and 80, except during the complication of appendicitis, when it rose slightly. The two episodes of acute appendictis were treated each with several days of intravenous feedings, without evidence of cardiac failure.

SUMMARY AND CONCLUSIONS

A patient with congenital heart disease, interventricular septal defect, at the age of 34 years developed an acute myocardial infarction. In spite of the complication of acute appendicitis and the necessary use of intravenous feedings for several days, on two occasions, the course of the acute cardiac illness was favorable and there was no evidence of cardiac failure. The electrocardiographic changes were characteristic of an acute posterior wall myocardial infarction. The ballistocardiogram was normal. This is the first report of an acute myocardial infarction in a patient with interventricular septal defect.

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TRICUSPID VALVE COMMISSUROTOMY WITH A ONE-YEAR FOLLOW-UP

HERBERT D. TRACE, M.D., CHARLES P. BAILEY, M.D., AND
MARTIN H. WENDKOS, M.D.

PHILADELPHIA, PA.

ALTHOUGH organic tricuspid valvular disease is considered to be a rare lesion,[1] it is our impression that it is more common than is generally appreciated. Its presence frequently escapes recognition by cardiologists and cardiac surgeons because the degree and the effects of tricuspid valvular disease are not sufficiently pronounced and may not always conform to the classical pattern. For this reason a report is made of an instance of successful tricuspid commissurotomy in a patient with a clinically recognized rheumatic tricuspid lesion presenting certain atypical features.

CASE REPORT

The case described is that of a 24-year-old white woman who was admitted for cardiac surgery to the Doctors' Hospital, Philadelphia, on April 21, 1952. During the two years prior to admission she had observed increasing fatigue and progressive diminution in exercise tolerance due to dyspnea. She had also observed, for several years, blueness of the fingers, and of her toes, in cold weather. At the age of 9 she had been hospitalized because of an attack of rheumatic fever and chorea. She denied any episodes of hemoptysis, orthopnea, or edema. She had had no attacks of paralysis or embolization.

Physical examination at the time of her admission revealed the following: She was a well developed, adequately nourished, white woman appearing younger than her stated age. She had no cyanosis about the face; her fingers were slightly blue without clubbing. Her toes were more blue than her fingers. There was no evidence of edema or ascites; no distention of the neck veins and no venous pulse were visible. Her hands and feet were cool and moist. The liver was not palpably enlarged. The blood pressure was 120/70 mm. Hg.

Auscultation of the heart revealed the presence of a gallop rhythm of the summation type and a systolic murmur near the cardiac apex. No murmurs other than the transmission of the apical systolic murmur were heard elsewhere over the precordium. There was no accentuation of the second pulmonic sound. A systolic thrill was palpable at the cardiac apex. A normal sinus rhythm was present.

Routine laboratory examinations were essentially negative except for the finding of considerable albumin in the urine. This finding was attributed to passive congestion of the kidney.

Radiologic studies revealed an absence of any cardiac enlargement except for the prominent convexity in the lower half of the right side of the heart due to right atrial enlargement and fullness of the right ventricular outflow tract (Fig. 1). A striking finding was the absence of enlargement of the left atrium as judged by the esophagram in the right anterior oblique position (Fig. 2) or the absence of the double festoon in the anteroposterior position (Fig. 1). It is to be noted that the bronchovascular markings in the anteroposterior view were present but not prominent.

From the Departments of Thoracic Surgery and Cardiology, Doctors' Hospital, Philadelphia, Pa.
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The routine electrocardiogram was a distinctly abnormal record (Fig. 3). The significant findings included: (1) increased magnitude and duration of the auricular deflections, (2) prolongation of the P-R interval, and (3) inversion of the T wave in the limb leads and lateral precordial lead.

Cardiac catheterization revealed no evidence of a shunt and no suggestion of a tricuspid lesion, as judged by the right atrial pressure readings.

Because of the still indefinite diagnosis and of the patient's symptoms and because one of us (M. H. W.) felt that surgical exploration of her heart was indicated on the supposition that this might be some atypical form of mitral regurgitation, preparations for cardiac surgery were carried out.

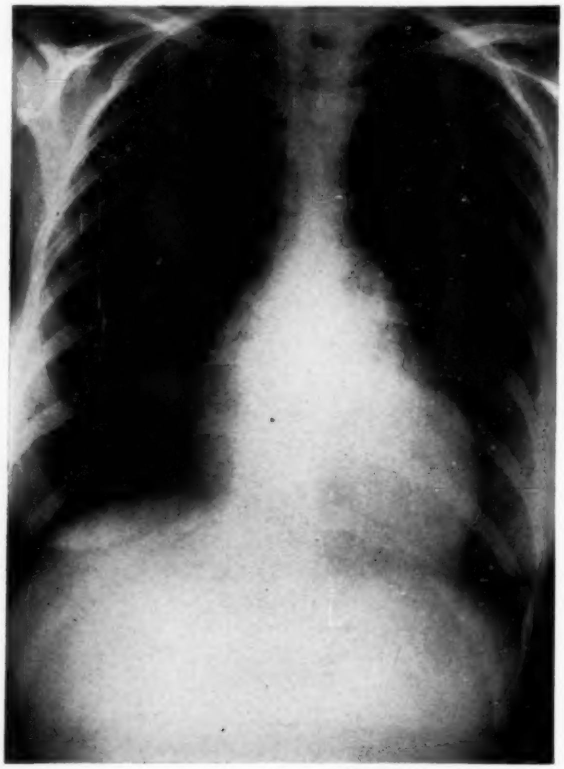

Fig. 1.—Roentgenogram of chest of 24-year-old white woman, anterolateral position, showing prominent convexity in lower half of right side of heart due to right atrial enlargement and fullness of right ventricular outflow tract.

On May 2, 1952, the first operative procedure was performed. The usual left posterolateral thoracotomy incision was made and extended through the fourth intercostal space. The heart, on palpation, was found to have a diastolic thrill over an area near the apex, the origin of which could not definitely be traced to the right or the left ventricle, but it was felt that it was probably over the right ventricle. A systolic thrill was present over the left atrium. The pulmonary artery was of normal size and without a thrill. The pericardial sac was somewhat distended and contained about 200 c.c. of normal looking pericardial fluid. The left atrium was found to be quite small. A purse-string suture was placed about the base of the left auricular appendage and was connected to a Rumel tourniquet, and a Trace-Bailey auricular appendage clamp was placed just distal to the purse string. The auricular appendage was opened and found to be free of clots, and the examining finger of the surgeon was then placed into the lumen of the left atrium.

It was found that the mitral valve, which would normally admit two fingers, would only admit one finger. In addition, there was evidence of regurgitation estimated at about 7 c.c. Commissurotomy with the knife was carried out on the anterolateral commissure of the mitral valve, and after this was completed, the mitral valve admitted one and one-half fingers, and there was present a regurgitation estimated to be about 4 c.c. No evidence of an interatrial septal defect was found. The left atrium was then closed. It was then observed that the auricular appendage of the right auricle was greatly distended and pointed directly toward the left. Its pulsations were noticed, and it was quite blue-purple in color. A purse-string suture was being placed about this appendage in order to explore it when the patient's heart became arrhythmic. It was deemed advisable to terminate the surgical procedure at this point. A rapid closure was made, and the patient had an uneventful postoperative course.

However, during the postoperative period, the patient's fingers and toes continued to be blue, cold, and moist but these symptoms were temporarily benefited by the administration of Priscoline.

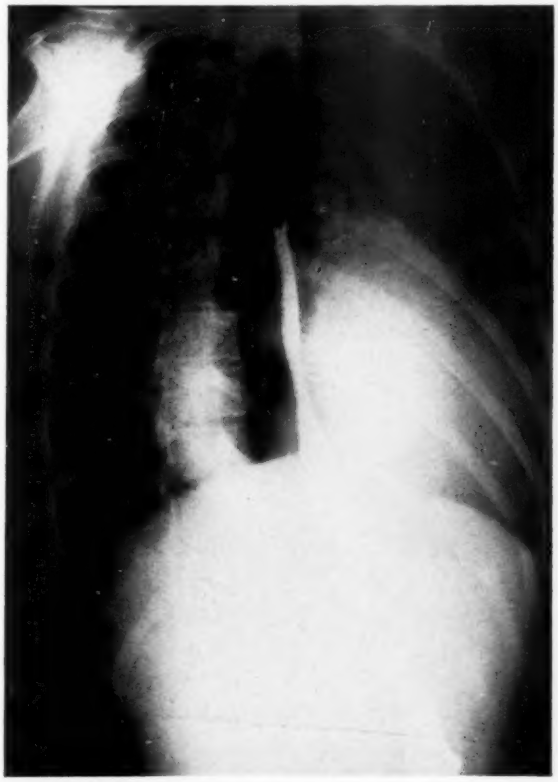

Fig. 2.—Esophagram of same patient, right anterior oblique position, showing left atrium to be apparently normal in size.

Two weeks after the mitral valve commissurotomy, surgical treatment of the tricuspid lesion was undertaken, the postoperative diagnosis of the lesion having been established by a venous pulse tracing which demonstrated the presence of prominent *a*, *c*, and *v* waves (Fig. 4). This time the patient was placed in the supine position, and the incision was made in the right fourth intercostal space extending from the sternum to the anterior axillary line. The ribs were retracted; the pericardium was opened and was found to have the bread-and-butter pericarditis which is so common several weeks after previous cardiac surgery. The right auricle was found to be very large. A purse-string suture was placed around the base of the appendage; a Satinsky clamp was

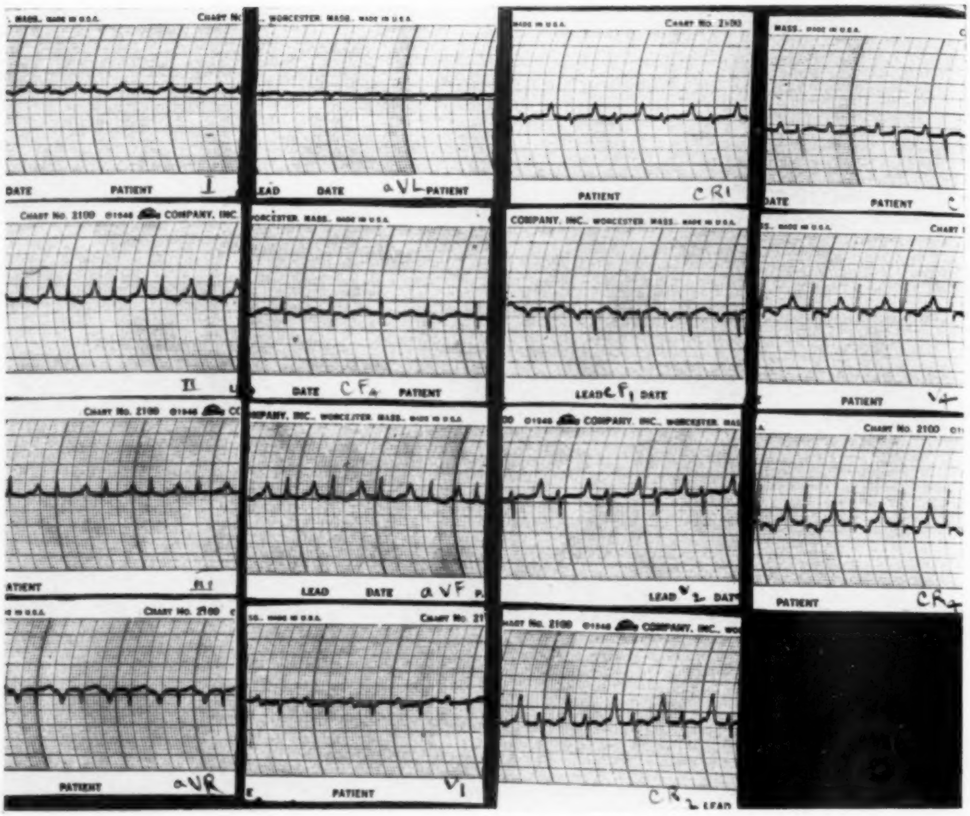

Fig. 3.—Electrocardiogram showing increased magnitude and duration of atrial deflections, prolonged P-R interval, and inversion of T wave in limb and lateral precordial leads.

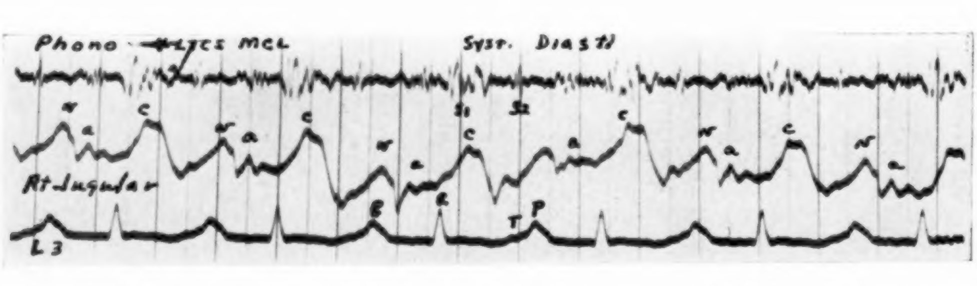

Fig. 4.—Venous pulse tracing following mitral commissurotomy, the prominent *a*, *c*, and *v* waves indicating the presence of tricuspid stenosis.

placed just distal to the purse string. The appendage was opened; blood was flushed out, and the left index finger of the examining surgeon was placed in the atrium, which was found to be voluminous. The superior vena cava seemed to be about one inch in diameter, and the inferior vena cava seemed to be about one and one-half to two inches in diameter. The exploring finger had a very difficult time trying to find another opening in this atrium. Finally, a tiny slit, 5 mm. in length, was found, and this was believed to be the tricuspid valve and not an interatrial septal defect. It was noted that this slit would not give on digital pressure. The right-sided heart knife was next inserted, and the anterolateral commissure of this valve was cut. This incision increased the opening but produced a regurgitation. It was felt that no further cutting in this direction would be advisable as it would tend only to increase the regurgitation. Therefore, the left-sided heart knife was inserted, and a slit was cut in the other direction. However, this slit also caused some regurgitation. After these two incisions, it was found that the valve admitted one and one-half fingers. The finger could readily be inserted into the right ventricle, which was quite small. At the conclusion of the commissurotomy, regurgitation from this valve was estimated to be 5 c.c. No further cutting of the valve to make the opening of normal size so that it would admit three fingers was attempted. The appendage was sutured; the pericardium was closed loosely; and the chest was closed.

The patient has made a good recovery. Follow-up examination a little over one year after surgery reveals that she is not short of breath and that she does not manifest orthopnea or edema. Her fingers and toes are not so blue as they were. There is still no evidence of a pulsation of the liver, or is there any evidence of pulsating jugular veins. She now does her household work without symptoms. Still present are a blowing systolic murmur over the mitral area and a mid-diastolic murmer in the same site. These murmurs are transmitted to the right of the sternum. The rhythm is normal. A roentgenogram of the chest taken one year after surgery shows the heart to be globular in shape and its configuration to be unchanged from that in the pre-operative roentgenogram.

DISCUSSION

The purpose of this report is to demonstrate that commissurotomy for acquired rheumatic triscuspid stenosis is feasible and that it can overcome the incapacities resulting from the lesion. With an increased awareness of its existence, it is likely that more such cases will be recognized and therefore benefited by proper surgical attack upon the valvular deformity.

The usual manifestations of organic tricuspid valvular disease include engorgement of the cervical and other segments of the systemic venous tributaries, enlargement of the liver with secondary cirrhotic changes in that organ as a result of long-standing congestion, ascites, and peripheral edema.[2] One may hear a systolic or diastolic murmur loudest over the lower sternal region especially on inspiration. Usually these murmurs will merge with the murmurs due to the mitral lesion and are therefore not generally ascribed to tricuspid stenosis.

Although the presence of an organic tricuspid lesion can be suspected on the basis of findings described here, confirmation of its existence must largely depend upon the demonstration of large *a* and *v* waves in the jugular pulse tracing and a presystolic wave in the liver pulse tracing, especially when normal sinus rhythm is present. In this case, such records were obtained even though the classical clinical features of tricuspid stenosis and insufficiency were absent. This experience therefore suggests that this relatively simple diagnostic procedure has probably not been sufficiently employed in appraising patients with chronic rheumatic heart disease.

SUMMARY AND CONCLUSIONS

1. A unique case of combined rheumatic tricuspid and mitral valvular disease exhibiting atypical features is described.

2. The correct pre-operative diagnosis established by venous and liver pulse tracings was confirmed at the time of surgery.

3. On separate occasions, successful mitral and tricuspid valve commissurotomies were performed, with alleviation of the symptoms resulting from the mitral and tricuspid stenosis.

4. The experience gained from this case indicates that multiple valvular stenotic lesions can be corrected by multiple commissurotomies.

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FUNCTIONAL MITRAL STENOSIS PRODUCED BY AN INTRA-ATRIAL TUMOR

WILLIAM LIKOFF, M.D., GEORGE D. GECKELER, M.D., AND JOHN E. GREGORY, M.D.

PHILADELPHIA, PA.

PRIMARY tumors of the heart are rare. Their infrequency is reflected in the medical literature which records, inclusive of 1948, but 348 cases.[1] Nevertheless, these tumors have excited considerable interest. This has been increased recently by the advances in cardiac surgery through which the removal and cure of certain of these neoplasms may be possible.

Benign cardiac tumors are three times as common as the malignant type. They are of mesoblastic origin, and include the myxoma, rhabdomyoma, fibroma, lipoma, angioma, leiomyoma, teratoma, and xanthoma. From a clinical standpoint, these tumors offer the greatest difficulty in diagnosis. They may give rise to features which are indistinguishable from ordinary forms of heart disease, or remain entirely obscure until discovered at post-mortem investigations. Occasionally, they may produce signs and symptoms sufficiently characteristic to permit an accurate ante-mortem diagnosis. Even in these latter instances, the atypical nature of the clinical course has been emphasized as the most helpful lead in establishing a diagnosis.[2]

The myxoma is the most common benign cardiac tumor. When it arises in the left atrium, is pedunculated, and overrides the mitral orifice, a functional stenosis of the mitral valve may be produced.[3,4] The present case report is an additional example of such a combination of events. It is of particular interest inasmuch as the intra-atrial tumor was not recognized preoperatively, in spite of precise cardiac study. Furthermore, the gross and microscopic examination of the tumor mass brings into focus again a much debated question: Are myxomata edematous, swollen forms of organized thrombi, or true neoplasms which originate from embryonic rests of mucoid tissue? Finally, it is probable that this case represents one of the few attempts at the removal of an intra-atrial tumor. The technique and slim margin by which it failed will be discussed by the surgical team in a separate communication.

CASE REPORT

M. D., a white woman of 33, was admitted to the Hahnemann Hospital on Sept. 7, 1950. She complained of extreme dyspnea with exertion.

From the Hahnemann Medical College and Hospital, Philadelphia, Pa.

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Four years prior to admission the patient developed a persistent cough, but it was not until 1949 that this symptom was attributed to a heart ailment. The interval from that date until the time of hospitalization was marked by frequent attacks of acute pulmonary edema and hemoptysis. Each of these was precipitated by exertion, and finally the patient was restricted to complete bed rest. Even under such restriction, dyspnea was marked.

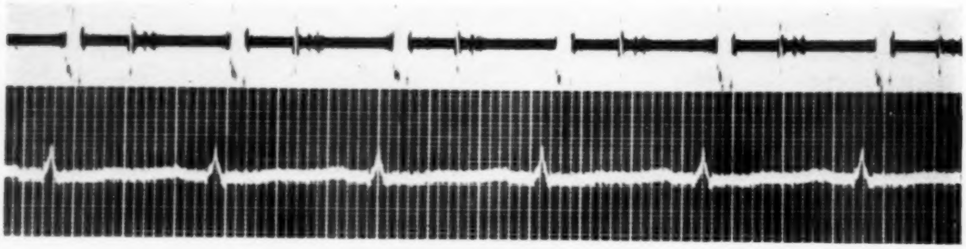

Fig. 1.—This phonocardiogram illustrates the mid-late diastolic murmur with its presystolic accentuation characteristic of mitral stenosis.

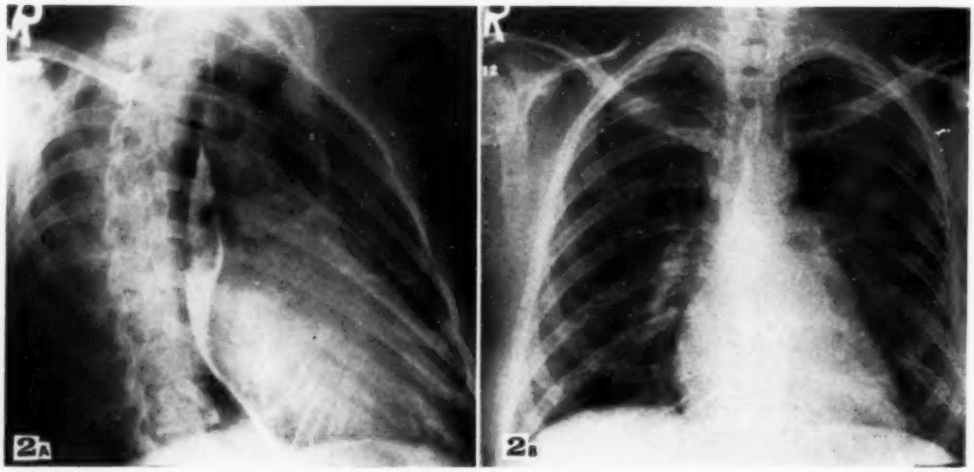

Fig. 2.—*A* and *B*. These roentgenographic pictures illustrate, in the right oblique, the posterior displacement of the barium filled esophagus by the enlarged left auricle, and in the posteroanterior view, the fullness of the pulmonary segment giving rise to a "mitralized" left cardiac border.

Although occasional episodes of migratory joint pains were experienced during childhood, the patient offered no definite history of rheumatic fever or chorea.

The youngest of the patient's two children was born 22 months prior to her present hospitalization. No unusual difficulty was encountered during that pregnancy. At no time did she observe peripheral edema or irregular heart action.

The abnormal physical findings were limited to the heart. Normal sinus rhythm was present. At the apex, a presystolic accentuation of a mid-late diastolic murmur typical of mitral stenosis was heard. The first heart sound was sharp, and the second pulmonic sound accentuated two plus.

Fig. 1 is a phonocardiographic illustration of the auscultatory findings described. Fig. 2 represents the teleroentgenogram, right anterior oblique, and posteroanterior projections of the heart. These were considered consistent with the configuration observed in mitral stenosis. Fig. 3 is an electrocardiogram, the features of which were the bifid P waves in Leads I and II and the inversion of the T waves in Leads II and III.

The urinalysis and complete blood count were within normal limits. The sedimentation rate was 38 mm. in one hour, the hematocrit 41 per cent, and the bleeding and venous coagulation times 1 and 7 minutes, respectively. The serology was negative, the blood urea nitrogen, 9 mg. per cent; the blood sugar, 103 mg. per cent; the total proteins, 7.6 mg. per cent; and the prothrombin time, 86 per cent of normal.

Cardiac catheterization was performed without difficulty and revealed the pressure in the main pulmonary artery to be 70/28 mm. Hg, in the right ventricle 80/6, and in the right auricle 6/2. After exercise the pressure in the pulmonary artery rose to 81/37 mm. Hg.

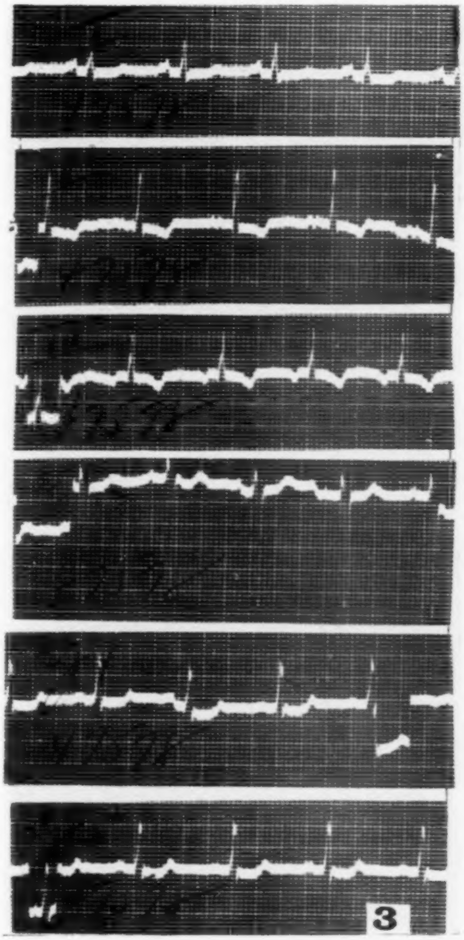

Fig. 3.—The electrocardiogram shows bifid P waves in Leads I and II and inversion of the T waves in Leads II and III.

A diagnosis of mitral stenosis with pulmonary hypertension was reached. Because of recurrent pulmonary edema and hemoptysis the patient was considered a proper subject for mitral commissurotomy.

At the time of operation, an enlarged pulmonary artery, right ventricle, and left auricle were discovered. However, on entering the left auricle a pedunculated tumor mass was palpated originating from the posterior inferior surface of the septum and from the posterior wall of the left auricle. The base of this protruding mass, resting as it did across the mitral orifice, effectively

Fig. 4.—This photograph illustrates the marked hypertrophy of the right ventricular wall.

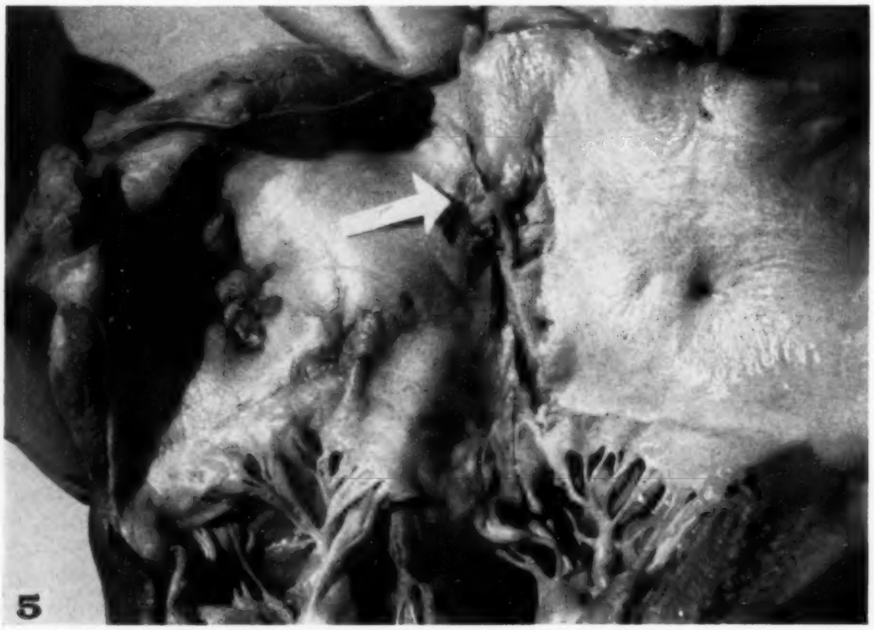

Fig. 5.—This picture of the mitral valve and left auricle clearly shows that although there are shortening and thickening of the valve leaflets and chordae tendineae there is by no means a significant valvular mitral stenosis. The thickened, white auricular endocardium is well shown. The arrow indicates the roughened area of attachment of the pedunculated, organized and organizing thrombus.

obstructed the flow of blood through the valve. With the exception of an apparent agglutination of the leaflets at the extreme angles, the mitral valve itself was normal.

The patient died shortly after the attempt at removal of this intra-auricular tumor mass. During the operation the tumor was fractured. The significant findings at autopsy were as follows:

The heart (350 grams) was enlarged due to dilatation of the left auricle, and right ventricle, and hypertrophy of the right ventricular wall (8 mm., Fig. 4). The lining of the left auricle was thickened and white and, near the foramen ovale, there was a roughened spot said, by the surgeon, to be the site of attachment of the mass (Fig. 5). The left auricular appendage had been recently opened and sutured. The mitral valve showed no gross changes indicative of stenosis or insufficiency. This valve and its chordae tendineae were thickened, with some fusion of the latter, but the valve was not greatly involved, and on reconstruction and manipulation appeared to be competent.

Fig. 6.—The photomicrograph shows the typical structure of the mass which obstructed the valve. It clearly appears to be edematous thrombus in the late stages of organization. The resemblance to edematous granulation tissue is striking.

Within the left ventricle were found several fragments of material entirely similar in gross and microscopic features to the mass removed surgically. A similar but much larger fragment (4 cm.) was found blocking the mid-thoracic aorta. The sections of this material and the surgical specimen showed organized and organizing thrombus. The organized portion was markedly edematous (Fig. 6). The site of endocardial attachment showed marked scarring and thickening of the endocardium with marked vascularization, changes usually considered compatible with chronic rheumatic endocarditis. No Aschoff bodies were present.

DISCUSSION

Nothing in the clinical picture, physical findings, or laboratory investigation in this patient suggested the possibility of an intra-atrial tumor producing a functional mitral stenosis. As previously noted, this is an extremely difficult diagnosis to establish. It may be suggested in patients with the auscultatory signs of mitral stenosis but with no history of rheumatic fever. However, such a combination of historical and clinical facts is encountered in over one-half of the patients with true mitral stenosis. In this particular case, a history of migratory arthritis during childhood was actually obtained, and the post-mortem examination revealed evidence of rheumatic endocarditis. It is apparent that the intra-atrial tumor coexisted with a minimal type of rheumatic heart disease, but that the obstruction of the mitral valve was mechanical, not inflammatory, in origin.

It has been suggested[3] that an intra-atrial tumor may be suspected under the following circumstances: when pain, palpitation, edema, and dyspnea are out of proportion to the degree of demonstrable heart disease; when the character of the mitral murmur is markedly altered by a change in body position; when extreme respiratory embarrassment results from certain changes in body position.

These distinctive features were not observed in this patient. The subjective symptoms were not inconsistent with the physical and roentgenographic examination of the heart, and the intracardiac pressure studies were in keeping with classical mitral stenosis.

The presystolic murmur remained constant when the patient was examined in the upright and recumbent positions. It may be assumed, therefore, that the tumor mass, because of its size and anatomic position, constantly obstructed the mitral valve. The fact that the attacks of pulmonary edema were clearly and only related to effort may serve as further evidence that the neoplasm was fixed in relation to the pulmonary veins as well. When this is not so, respiratory difficulty develops with transitory blockage of the inflow of the pulmonary veins by the mobile neoplasm, this most characteristically occurring with changes in body position.

It is apparent that when an obstructing intra-atrial tumor maintains a more or less fixed, positional relation to the mitral valve and pulmonary veins, the two fundamental clinical features of the condition may not be present.

In the past,[5-9] the occurrence of unexplained periods of cardiac decompensation, arrhythmias, and bizarre conduction defects, and atypical clinical courses has been emphasized as suggestive of the diagnosis of a tumor of the heart. The case under discussion demonstrates that neoplasms may be found in the face of conventional historical and clinical findings.

The microscopic examination of the tumor suggests it was a well-organized thrombus. It is believed by some that all myxomata are degeneration forms of organized thrombi, or of thrombi in various stages of organization. The opposing view holds that they spring from embryonic mucoid tissue and are true neoplasms. Since this patient had rheumatic endocarditis, it is most probable that a thrombus formed along a portion of the diseased auricular endocardium, subsequently, became pedunculated and obstructed the mitral orifice.

SUMMARY

1. A case of functional mitral stenosis produced by an intra-atrial tumor is presented.

2. Examination of the tumor and the clinical background of the patient suggest that it was an organized pedunculated thrombus originating from the wall of the left atrium.

3. Precise study revealed that the mitral stenosis was caused by an obstructing tumor and not rheumatic endocarditis.

4. The classical evidence for an obstructing intra-atrial tumor may be absent when the mass is relatively immobile.

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ABERRANT CONDUCTION IN SUPRAVENTRICULAR EXTRASYSTOLES ELIMINATED BY EXERCISE

WILLIAM S. BOIKAN, M.D., F.A.C.P., AND ROLF M. GUNNAR, M.S., M.D.

CHICAGO, ILL.

IT HAS been shown that aberrant conduction in premature auricular systoles may be a physiologic phenomenon.[1-4] Sir Thomas Lewis[5] demonstrated that the recovery curve of the conducting tissue normally begins earlier as the heart rate increases, and that the recovery curve depends on the length of the preceding cycle. This means that the refractory period is roughly proportional to the length of the cardiac cycle. Sherf[4] and Gouaux and Ashman[1] used this phenomenon to explain the aberration which may occur clinically when a beat with a short R-R interval occurs after beats of a longer cycle. In this case the long cycle determines a long refractory period and the impulse arriving from the succeeding short cycle meets a refractory conduction system. The refractoriness frequently manifests itself only in one bundle and usually in the right, giving aberration with the picture of right bundle branch block.

Apart from this physiologic phenomenon, aberration may be produced in premature beats of supraventricular origin because of disease of the conducting tissue. It has been shown in the experimental animal that aberration of premature beats may be the only electrocardiographic sign of disease of the specialized tissue[6]. Vesell[7] emphasized that aberration may be due to exceeding the "critical rate" for the normal propagation of the impulse—that the diseased bundle branch required a longer refractory period than the normal branch. Therefore, after a certain rate is passed, the diseased branch remains refractory and is no longer able to transmit the impulse. It is then transmitted down the still functioning bundle and later across the septum as in bundle branch block.

It is then possible that in an otherwise normal electrocardiogram, auricular premature systoles with aberrancy may represent either a normal phenomenon (Ashman phenomenon), or may represent the early evidence of disease, carrying the same significance as intermittent bundle branch block. However, it seems possible to separate the two phenomena by increasing the heart rate. The preceding cycle would thus be shortened and in the normal heart the recovery of the conducting tissue would begin earlier[5] and conduct the premature beat normally. In the diseased heart where the aberration is due to exceeding the "critical rate,"[7] the block should persist, increase, or even occur in the sinus beats, but not disappear.

From the University of Illinois, Department of Medicine, and The Cook County Hospital, Department of Medicine, Chicago, Ill.

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CASE REPORT

E. R., a 44-year-old male was referred to one of us (W.S.B.) in March 1953, because of palpitation. In 1946, he had detected an irregularity in his heart associated with a feeling of fullness in his chest. He was told at that time that he had heart disease. At yearly examinations he was told his heart was worse, but he continued working. Electrocardiograms, in 1948 and 1950, were reported as normal. On questioning, there was no dyspnea, no effort pain, orthopnea, cough or edema, and no symptoms referable to the heart other than consciousness of the premature beats.

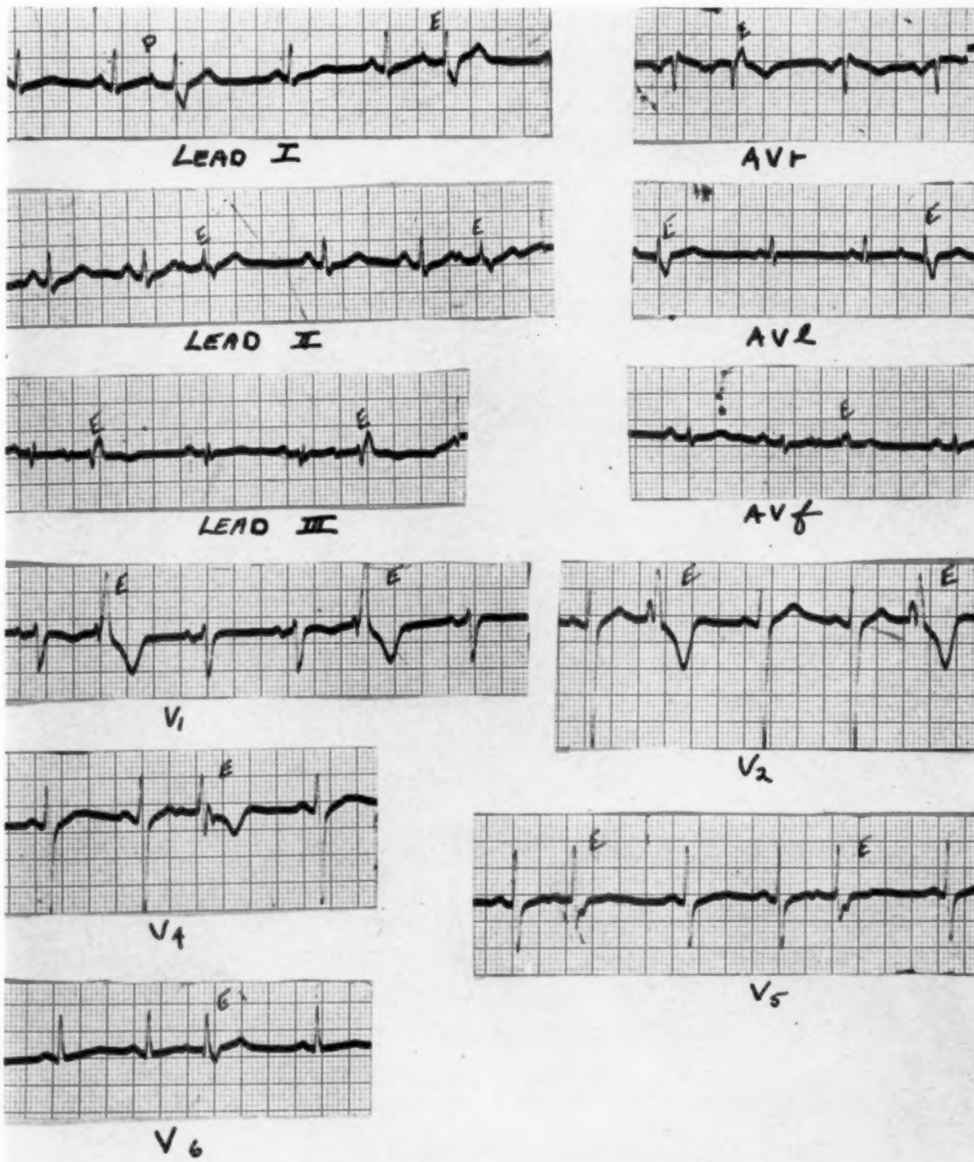

Fig. 1.—Electrocardiogram taken at rest showing supraventricular extrasystoles with aberrant conduction of the right bundle branch type.

Physical examination revealed a thin, somewhat nervous white man appearing generally in good physical health. His thyroid was palpable but not enlarged. The heart was of normal size. Heart tones were normal and there were no murmurs. Laboratory data were all normal. The electrocardiogram (Fig. 1) showed frequent supraventricular premature beats with right bundle branch block. After 135 two-steps, another electrocardiogram (Fig. 2) showed that the rate was increased

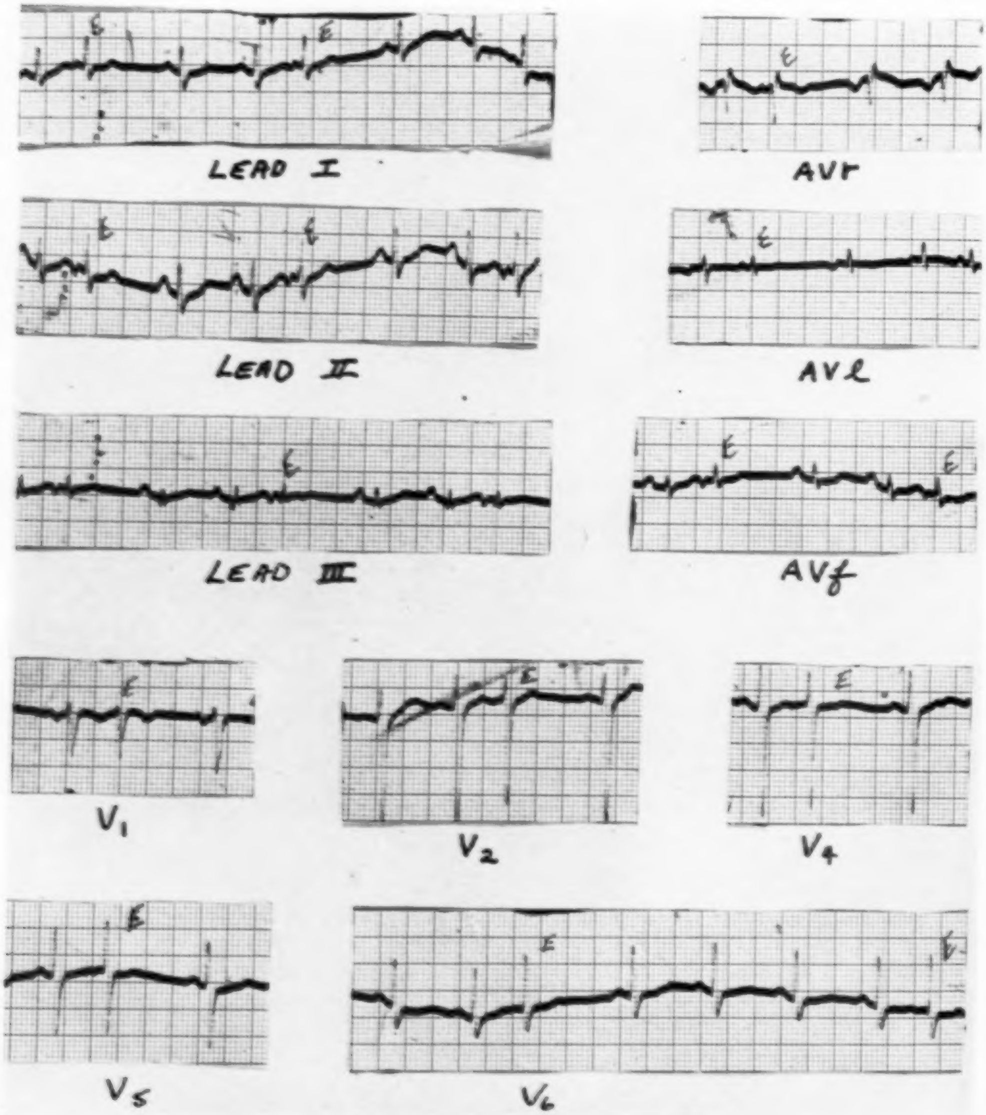

Fig. 2.—Electrocardiogram taken immediately after 135 two-step test showing persistence of the supraventricular extrasystoles but disappearance of the aberrant conduction.

from 83 per minute to 111 per minute, and the premature beats, although still present, were normally conducted. The R-R interval had decreased from 0.72 sec. to 0.54 sec. and the R extrasystole R interval had decreased from 0.46 sec. to 0.36 sec. The loss of aberrant conduction indicated that this patient had a normal conduction system.

SUMMARY

A patient with premature supraventricular systoles associated with aberrant conduction of the right bundle branch type was exercised. The increase in the heart rate caused the aberrancy to disappear showing that the patient had a normal conduction system. This indicated that the aberration was the manifestation of a normal physiologic phenomenon and not an early sign of disease.

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TEMPORARY ATRIOVENTRICULAR CONDUCTION DISTURBANCE ASSOCIATED WITH INGESTION OF VERATRUM VIRIDE

BARNETT ZUMOFF, M.D.*

SAN ANTONIO, TEXAS

A NUMBER of recent reports have focused interest on the autonomic factors influencing atrioventricular conduction in the human heart. It has been shown that changes in autonomic tone associated with respiration or changes in posture can have marked effects on conduction[1-3] and that emotional factors may also produce definite aberrations.[4] The purpose of the present case report is to present an instance in which "functional" changes in cardiac conduction were apparently the result of ingestion of a powerful autonomic drug, the vagomimetic substance veratrum viride.

CASE REPORT

On Dec. 6, 1952, C.H.R., a healthy 19-year-old aviation cadet was given a physical examination to determine his qualification to undertake pilot training. The examination findings were all normal, except for a slight elevation of blood pressure. As prescribed by regulations, morning and afternoon blood pressure readings were obtained for three consecutive days as a check. The average blood pressure readings for the three-day period were 144/88 mm. Hg in the sitting, 142/90 in the recumbent, and 144/92 in the standing positions. Because these values were above the limits prescribed by regulation, the examinee was physically disqualified.

Following this, the examinee, unknown to Air Force medical authorities, consulted his family physician. The latter prescribed Verutal† for the lowering of the examinee's blood pressure. During the period from Dec. 23, 1952 to Jan. 20, 1953, the examinee took two Verutal tablets daily, with only an occasional dose omitted. After this period, the examinee discontinued the medication permanently, since he felt that it was of no benefit.

On Feb. 5, 1953, the examinee took and passed a physical examination for entrance into Air Force Officer Candidate School. The blood pressure readings on this examination were normal. However, because of the previous mild blood pressure elevation, it was suspected that the examinee might have been taking medication to lower his blood pressure. Accordingly, electrocardiographic tracings were obtained in an attempt to detect drug effects.

The electrocardiograms obtained on Feb. 5 (Fig. 1) showed a marked conduction disturbance, interpreted as an intermittent wandering of the cardiac pacemaker downwards from the sinus node to a focus in the right Bundle of His, producing a pseudo-left bundle branch block. This disturbance was not affected by changes of position or by phase of respiration, or by carotid sinus pressure. It was felt that it might well result from the action of a vagomimetic drug such

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From the Aviation Medical Service, 3700 Med. Gp., Lackland AFB, San Antonio, Texas.

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*Present address: 373 Avenue S, Brooklyn, N. Y.

†Verutal (Rand Pharmacal Company)—each tablet contains veratrum viride 100 mg., mannitol hexanitrate 32 mg., rutin 10 mg., and phenobarbital 15 mg.

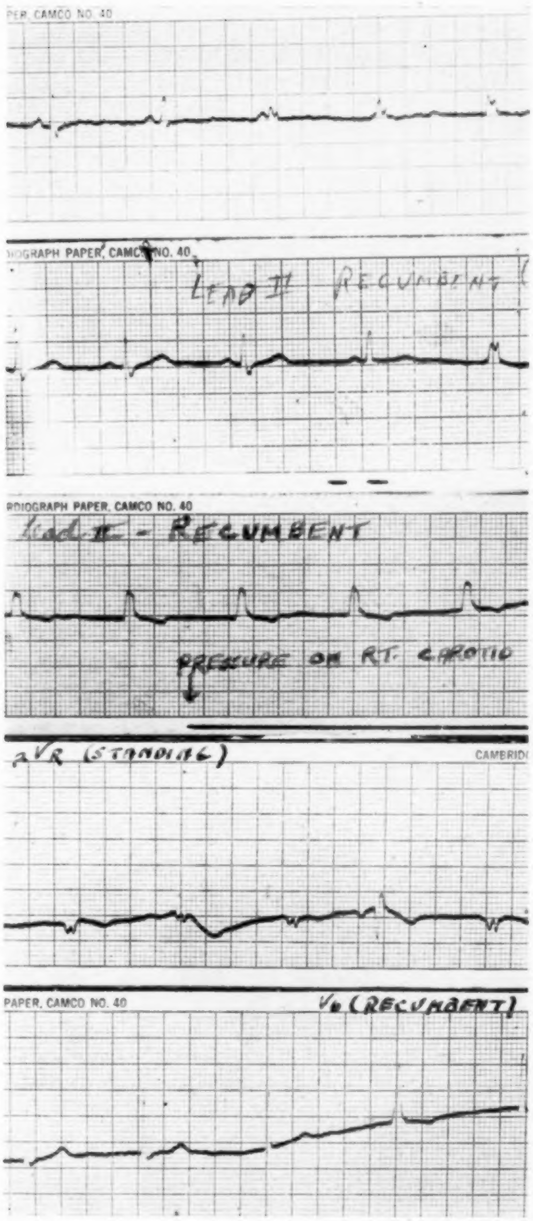

Fig. 1.—Tracings obtained on Feb. 5 and 6. There were no qualitative differences in the type of aberration on the two days, only a decreased frequency on the second day; therefore, the strips shown are selected at random from the tracings of both days. *A* shows a typical transition from normal to abnormal rhythm, with a gradual shortening of P-R interval in successive complexes, followed by the disappearance of P waves and the appearance of a "ventricular type" of QRS complex. *B* is another example of the same transition. *C* shows a group of abnormal complexes, and illustrates the lack of effect of carotid sinus pressure. *D* shows a group of abnormal complexes with a momentary lapse to a normal rhythm, followed by a return of abnormal complexes. *E* shows a group of normal complexes, with a momentary lapse to the abnormal rhythm, followed by a return to normal rhythm. The abnormal complex, in lead V_6, shows an upright, widened complex with a delayed intrinsicoid deflection, identifying the disturbance as a (pseudo) left bundle branch block. The gradual shortening of the P-R intervals without change in R-R interval is diagnostic of downward wandering of the pacemaker; the absence of P waves when the widened complexes are seen suggests that the pacemaker is below the atrioventricular node at that time. The total picture is a downward wandering of the pacemaker into the right bundle of His, producing a pseudo-left bundle branch block.

as veratrum viride, which the examinee now readily admitted taking. Although the last dosage of drug was 15 days prior to the date of this electrocardiogram, it was considered possible that some residual drug effect might still be present. With this in mind, another set of electrocardiographic tracings was obtained on Feb. 6. These tracings showed essentially the same conduction disturbance, but somewhat less pronounced. A third and final set of tracings was obtained on Feb. 26, and these showed no trace whatever of the previously observed disturbances. Thus, it was felt that the original impression of a drug effect gradually wearing off was correct.

During this period of electrocardiographic study, two three-day blood pressure rechecks were performed: from Feb. 4 to 6, and from Feb. 24 to 26. All blood pressure readings, in all positions, were normal on both these rechecks. It was concluded that no hypertension was present, and therefore the examinee was physically qualified.

DISCUSSION

The occurrence of electrocardiographic disturbances and the history of drug ingestion in this case are factual. The cause and effect relationship between the two is inferential but is made likely by the temporal relationships and by the agreement of the type of disturbance with the known physiologic properties of veratrum viride. It was considered somewhat surprising that a veratrum effect should persist as long as two weeks, but the present case seems to suggest that such may be true at times. It is possible that the subject of this case report was somewhat hypersensitive to the effects of veratrum, since the electrocardiographic disturbances produced in him have not been described previously. This type of conduction disturbance is occasionally seen as a transitory phenomenon during carotid sinus pressure, presumably mediated by vagal impulses to the heart. Thus it is consistent for a vagomimetic drug such as veratrum to elicit the observed aberrations.

That no true hypertension was present in this individual seems beyond doubt. Perhaps the very absence of hypertension, the usual therapeutic indication for veratrum, may account in part for the unusual type of effect. Since many individuals manifesting hypertension, as arbitrarily defined, are not true hypertensive patients, or at least are in a very early, labile stage of hypertension, it seems possible that the ingestion of veratrum by these individuals might produce somewhat different effects from those produced in true hypertensive patients. Another possibility in this individual is a role played by anxiety in sensitizing the heart to the effects of autonomic drugs. Since anxiety alone can affect the conduction mechanisms, one might expect synergism between anxiety and autonomic drug effect on the conduction system.

In view of the probability that a drug effect was demonstrated, it would seem worthwhile to check the electrocardiograms of individuals suspected of taking medication to bring down a slightly elevated blood pressure, a practice which undoubtedly is not unheard of among highly motivated physical examinees, such as aviation cadets or applicants for life insurance.

SUMMARY

A case is described in which the ingestion of veratrum viride, in an attempt to lower the blood pressure, apparently produced definite electrocardiographic

conduction disturbances, namely downward wandering of the cardiac pacemaker from the sinus node into the right bundle of His, producing a pseudo-left bundle branch block. The physiologic mechanisms are discussed, and it is suggested that this disturbance may be found in others who take veratrum to lower blood pressure and may be useful in detection of its unacknowledged use.

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Book Review

Das Strömungsgesetz Des Blutkreislaufes. By Karl Wezler and Werner Sinn. Editio Cantor Aulendorffi. Württemburg, 1953, pp. 126, 36 figures.

This monograph is, in a way, the culmination of Wezler's work in Otto Frank's laboratory extending over 20 years. Starting from the validity of Poiseuille's model experiments in application to peripheral circulation, the role of complicating factors such as viscosity, character of the blood suspension, pressure variability, and most important, elasticity of the arterial wall, is discussed and investigated. In spite of large differences in various perfusion preparations, the flow-pressure relationship can be expressed by a simple exponential equation, in which the functional state of the vessel is characterized by the value of the exponent (> 1.0 contracted, < 1 dilated). The authors arrive at a single, though rather complex equation, incorporating all factors found to be of importance for the resulting peripheral blood flow. For instance, the change of the length of the vessel with blood pressure is considered in addition to changes in diameter. The equation, "the law of flow of the blood circulation", is tested and confirmed in animal experiments (lung preparations) under various experimental conditions.

The significance of these results for the interpretation of blood flow experiments is illustrated in selected examples from the literature. It is shown, for example, that even such a competent author as H. Rein misinterpreted his experiments on the effect of atropine on coronary circulation. The application to the definition of the "total peripheral resistance" is also of interest.

The book will contribute to a more precise analysis of peripheral circulation and is recommended for all interested in the fundamentals of this complex field. It is, in the best sense, a continuation of O. Frank's work.

E. S.